FEBRUARY 1955

BULLETIN

OF THE NEW YORK ACADEMY OF MEDICINE

Original Articles

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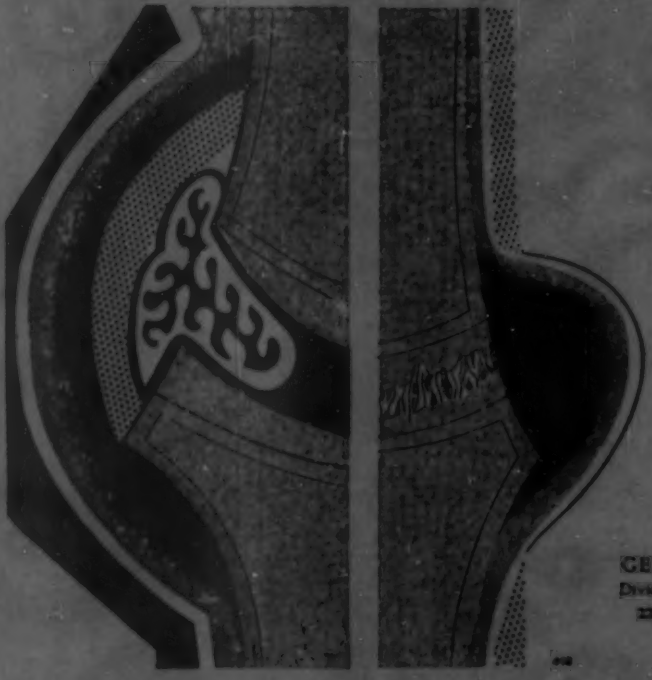

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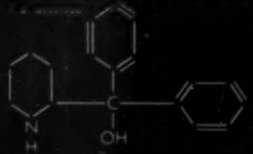

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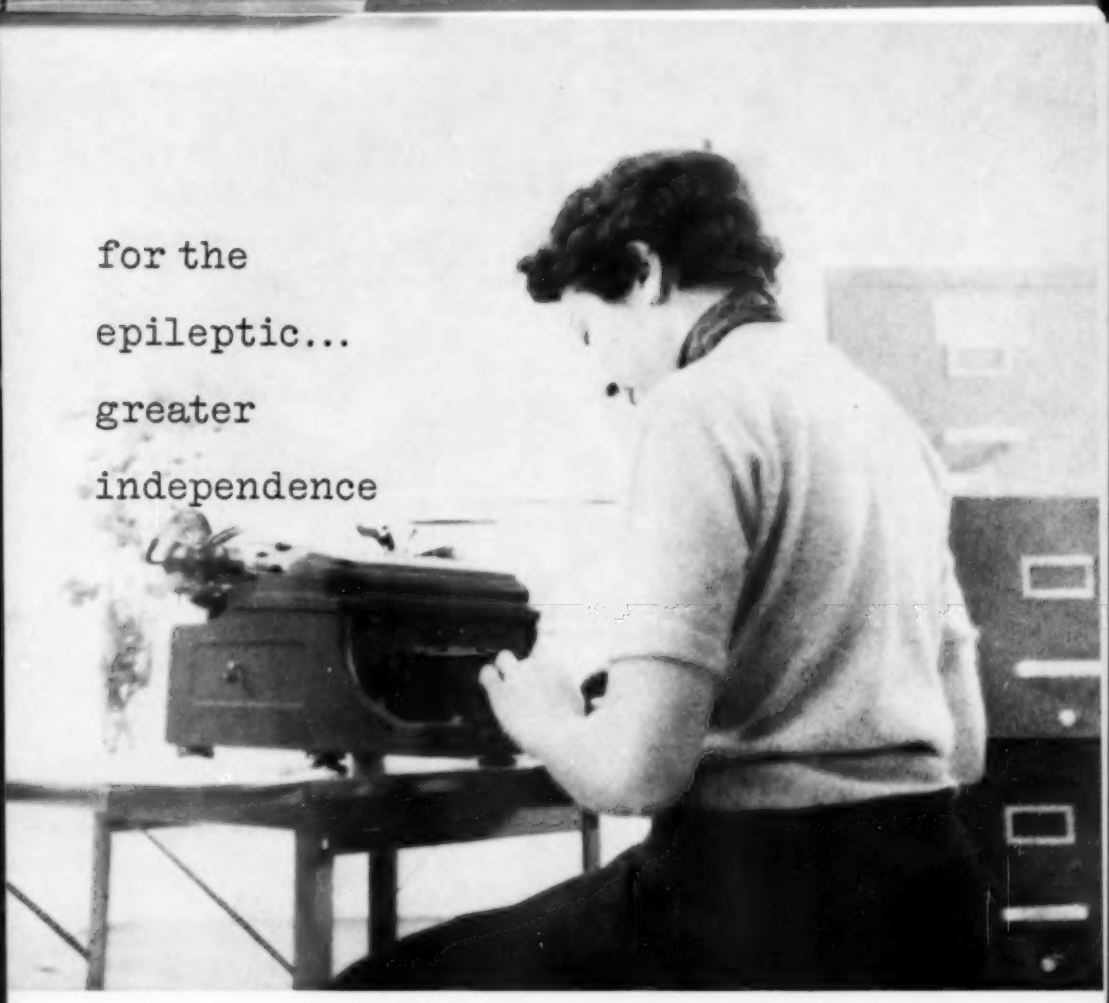

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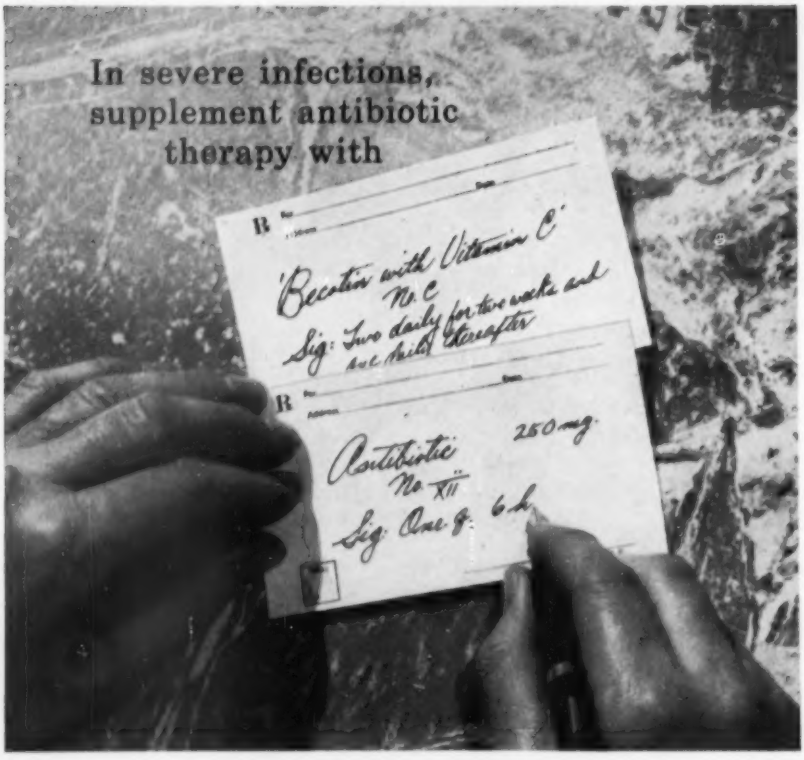
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ROBERT L. CRAIG, *Editor*

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BULLETIN OF
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VOL. 31, NO. 2 FEBRUARY 1955

THE CHANGING PATHOLOGIC PICTURE OF INFECTION SINCE THE INTRODUCTION OF CHEMOTHERAPY AND ANTIBIOTICS*

PAUL R. CANNON

Professor of Pathology and Chairman, Department of Pathology, The University of Chicago, Chicago, Ill.

THE pathologic picture of infection of the past few years presents a striking contrast to that seen before the introduction of chemotherapy and antibiotic treatment. In fact some frequently lethal diseases which were treated so ineffectually prior to 1940 have now become essentially nonlethal, and their virtual elimination as a cause of death has materially modified the practice of pathology. As lobar pneumonia, purulent meningitis, mastoiditis, puerperal sepsis, septicopyemia, venereal disease and others have gradually vanished from the necropsy room, life in the morgue has become correspondingly placid. Although the younger pathologist may still fear tuberculous infection mainly because he is himself tuberculin-negative, he knows that as a rule the consequences of postmortem infections are no longer apt to be serious. In short, if

* Presented at the 27th Graduate Fortnight of The New York Academy of Medicine, October 19, 1954.

his professional life is not more cheerful because of the replacement of infectious processes by those of neoplastic, cardiovascular or viral nature, or because of exposure to radioactive tissues, it is at least less hazardous. Even the once-common terminal pneumonia, that preantibiotic "friend of the aged," is seen less often, so that at times one wonders about the mounting therapeutic obstacles to the very act of death itself.

It is not surprising, therefore, that these changing pathologic patterns have raised in some minds the hope that we may be seeing at least the beginnings of man's final conquest of infectious disease as a killing agent. Before accepting this happy view, however, it would be well to keep in mind the unhappy fact that many infectious agents possess a remarkable adaptive capacity for survival. Moreover, chemotherapy and antibiotic treatment operate under a serious handicap in that usually they are forced to await the onset of the disease before they are clinically applied. From that standpoint antibiotic therapy suffers by comparison with those measures of preventive medicine which, in this country at least, have almost eliminated smallpox, diphtheria and tetanus and have taken to a large extent from our environment the hosts of pathogenic agents which, only a few years ago, were of such general concern. It may be, nevertheless, that one of the great indirect benefits of chemotherapy and antibiotic treatment has been the "purification" of many dispersers of pathogenic cocci, particularly streptococci and pneumococci as well as other microbial types, thereby reducing the infectious hazards of daily life and of the air we breathe, including that of hospitals. This statement must be qualified, however, with respect to staphylococci, where evidence of the emergence of antibiotic-resistant strains in hospital populations has even led to the use of the term "hospital staphylococci."

Despite the spectacular accomplishments of antibiotic therapy we all know that it has brought with it new problems. Increasing concern continues to be expressed about the appearance of resistant strains of bacteria, and of superimposed infections presumably activated by alterations in bacterial ecology accompanying antimicrobial therapy. The problems of drug reactions are also continually present, and magnified by the injudicious use of antibiotics for minor maladies. Nevertheless, despite these pressing problems, it would be indeed unfortunate if overemphasis of their importance should engender an unduly cautious attitude toward chemotherapy and thus tend to minimize the gains which have so modified the pathologic aspects of infection. In short, to the

extent that there is concern over the problem of antibiotic resistance, this will warrant greater apprehension only when the resistance applies to all antibiotics now available or to be made available, or when the resistant strains also manifest an increased pathogenicity. Certainly as yet this does not seem to be the case. Moreover, even though the increasing frequency of drug sensitizations leads too often to serious toxic manifestations, such as acute anaphylaxis, granulocytopenia, anemias, arteritis, myocarditis and so forth, at least information is steadily accruing which may help to eliminate or to minimize the severity of many of these complications. As Turell and Maynard[1] have recently emphasized: "The intelligent clinician is neither influenced nor deterred by the possible side-effects when there is a clear-cut indication for the use of an antibiotic," because he knows that an "exaggerated fear of complications may lead to ineffective therapy."

Probably the complication of greatest current interest is that of the development of superimposed infections as a result of antibiotic suppression of drug-sensitive microorganisms and the concomitant emergence of drug-resistant strains. As a consequence we are confronted, in increasing frequency, with infections associated with fungi, staphylococci, and of pseudomonas and proteus types, all resistant to most of the antibiotics now in use. These resistant microorganisms, although as a rule not highly pathogenic, seem as a result of antibiotic action to find tissues more favorable for growth and spread and to be responsible at times for generalized or terminal infections. Efforts to ascertain the reasons for these altered microbic interrelationships have led to varying suggestions, for example, to changes in the bacterial flora of the respiratory or digestive tract whereby vitamin synthesis is inhibited, to antibiotic stimulation of the ordinarily insensitive strains to greater growth or metabolic activity, or to a disturbed balance of nature through a shifting of the normal checks and balances which seem to regulate the bacterial flora itself. Thus, Miller and associates have recently demonstrated an increased susceptibility of mice to infection with a streptomycin-resistant strain of S. enteritidis following preliminary treatment by mouth with a large dose of streptomycin, due, in their opinion, to "a disturbance of the normal intestinal microflora by the antibacterial action of the drug."[2]

At the present time a great deal of attention is being centered upon the problem of the rising frequency of monilial infections in relation to

antibiotic therapy. Although not questioning the fact itself, several investigators have pointed out that in many instances this occurs in debilitated patients with malignancies, especially leukemia or Hodgkin's disease, and particularly in relation to a developing leukopenia or granulocytopenia. In a careful analysis of the problem Kligman[3] has suggested that under these circumstances the pathogenic potentialities manifested by the yeasts are not necessarily due to antibiotic stimulation but may be a consequence of the depressed antimicrobic resistance of the disease itself. Likewise, the superimposition of infections by pseudomonas or proteus organisms may at times have a similar relationship to antibiotic therapy. At any rate, in the latter types of infection other antibiotics are often able to restrict the growth of these bacterial types, and even with fungus infections, one of the newer antibiotics may help to minimize the superinfection caused by these microbial types.

Some aspects of this general problem are seen in the case of a twenty-eight year old woman under treatment for lymphosarcoma. The patient had had a persistent leukopenia of about 2000 leukocytes per cmm., and about one month before her death, while receiving nitrogen mustard therapy, she developed a pancytopenia with a total leukocyte count of 650 per cmm. Coincidentally her blood culture became positive for E. coli. Chloramphenicol was given and the blood became sterile a few days before death. Necropsy revealed a markedly hypocellular bone marrow and a disseminated moniliasis affecting particularly the lungs, peritoneum, pancreas, heart, and kidneys.

At first glance this would seem to be an example of the activation of a yeast infection by an antibiotic. It is important to note, however, that about two weeks before death the patient's total plasma protein concentration was 4.24 grams per 100 ml. of blood. Obviously the patient while developing the pancytopenia and the E. coli bacteremia was also severely debilitated. It seems reasonable to suppose, therefore, that she might have succumbed earlier to the E. coli infection had not the chloramphenicol cleared up this, thereby setting the stage for the terminal infection by monilia. From this point of view, therefore, the yeast infection was purely adventitious.

More unusual but illustrative of the basic problem of antimicrobic resistance in relation to chemotherapy is the case of a forty-eight year old man who was under treatment for myelogenous leukemia. About five weeks before his death he was given nitrogen mustard therapy fol-

lowing which he developed a fever of undetermined nature. One week before death his total plasma protein concentration was 4.97 grams per 100 ml. of blood. Penicillin treatment was started but death occurred two days later. Necropsy disclosed a massive tuberculous pneumonia and a generalized miliary tuberculosis with indescribably large numbers of acid-fast bacilli in the various lesions. Obviously the cause of the tuberculous generalization was not the antibiotic treatment. A more reasonable explanation is that it was related to the loss of resistance accompanying the debility of the disease and added to by the toxic effects of the nitrogen mustard. If penicillin had been given over a longer period, however, the question of superimposed infection due to antibiotic stimulation might well have been raised.

The problem of superinfection with pseudomonas organisms accompanying antibiotic treatment is illustrated by the case of a fifty-five year old man under treatment for aleukemic leukemia. When first seen in our clinic his leukocyte count was 1000 per cmm., and a sternal biopsy revealed a fibromyxomatous marrow. The leukopenia persisted, usually below 1000 leukocytes per cmm. For about three weeks he received daily injections of ACTH, together with large amounts of penicillin and streptomycin. The day after the ACTH treatment was stopped he developed a fever and a cellulitis of the left forearm, and a blood culture was positive for pseudomonas. Despite continued use of the antibiotics his condition worsened and five days before death his total leukocyte count was 700 cells per cmm. Necropsy disclosed multiple renal abscesses, an abscessive pneumonia, and an almost completely aplastic bone marrow. Here, again, the inference is that a microorganism of low pathogenicity but resistant to penicillin and streptomycin was able to manifest pathogenicity in a debilitated subject whose hypocellular bone marrow could no longer function adequately to sustain antibacterial resistance.

A final illustration of the importance of the hemopoietic system in relation to chemotherapy and antibiotic treatment is seen in the case of a five-year old child under treatment for a stem cell leukemia. Over a period of five months he received injections of aminopterin together with large quantities of sulfonamides and a variety of antibiotics, as well as many blood transfusions. Throughout the course of treatment he had leukopenia, in the final weeks with a leukocyte count of from 300 to 600 cells per cmm. Finally he developed a high fever and jaundice and died. Necropsy disclosed a cell-poor, edematous bone marrow, gan-

grenous and mycotic ulcers of the small bowel, monilial and coccal masses in many abdominal veins, and microinfarcts of the liver containing coccal and monilial masses. Here, again, the depressed antimicrobic resistance of the disease and a prolonged granulocytopenia coupled with extensive use of antibiotics presumably afforded an excellent opportunity for monilia and cocci to grow terminally.

Despite the emphasis upon depressed resistance of the host as a major factor making possible the appearance of infections often attributed to antibiotic activation, it obviously cannot explain the situation in which resistant staphylococci gain dominancy in the digestive tract in the course of antibiotic therapy in non-debilitated patients. The condition associated with this transformation of the intestinal flora is now of especial interest to surgeons, under such names as toxic enterocolitis, pseudomembranous enterocolitis, staphylococcic gastroenterocolitis, staphylococcus enteritis, etc. Although generally assumed to be a complication of antibiotic therapy, the condition was known before antibiotics came into use. In any event, recent reports tend to favor the view that the symptoms are due to bacterial predominance in the bowel of staphylococci capable of secreting an enterotoxin of the type long studied by Dack and shown to be an active agent in acute food poisoning. Such a toxin can account for the symptoms of nausea, vomiting, diarrhea, and in the more serious cases, for the shock-like state. It can also account for the favorable effects of ACTH therapy, as reported by Prohaska et al.[4]

Several excellent studies of this condition have been reported recently, particularly by Terplan et al. from Buffalo,[5] by Reiner, Schlesinger and Miller from Boston,[6] and by Fairlie and Kendall from Hartford, Conn.[7] In the eight fatal cases studied by Terplan and associates, all from postsurgical patients who had been treated with broad-spectrum antibiotics, it was shown in a few instances that the micrococci isolated from the bowel were insensitive to the antibiotics which had been used but were sensitive to erythromycin.

In addition to this type of pathologic alteration presumably related to antibiotic treatment, there is increasing evidence of a rising incidence of staphylococcic infections, manifested as wound infections, bacteremia, pyemia, endocarditis, bone infections and the like. Spink[8] and Herrell, Nichols and Martin,[9] among others, have recently discussed this problem with particular reference to the usefulness of erythromycin and other antibiotics in combating the resistant strains of micro-

cocci. It should be re-emphasized, however, that evidence is lacking so far as I am aware, that the antibiotic-resistant staphylococci themselves have become more pathogenic. It would seem, rather, that only their normally competitive environment has been interfered with in consequence of which they no longer are subjected to the usual mutual restraints characteristic of bacterial antagonisms. This would merely seem to be another instance in the biological world of interference with a balance of nature, or in this case, with microfloral homeostasis.

Despite these special instances illustrative of some of the complexities of antibiotic therapy, the beneficial effects of chemotherapy and antibiosis have been so amply demonstrated in recent years that it seems almost gratuitous to present additional evidence of their beneficent role. However, there is a finality about morgue data that offers advantages over some of the uncontrollable variabilities of clinical observation. Perhaps it is now time, therefore, for pathologists to analyze their data from various points of view in order to take an overall "look at the record." Bell[10] has recently done this with reference to the decline in the mortality from syphilis in Minnesota on the basis of deaths recorded at necropsy between the years 1931 and 1953 from the pathology services of the University of Minnesota. In his analysis only lethal lesions were included, principally those of syphilitic aortitis and neurosyphilis. His figures led him to the conclusion that the mortality from this disease in Minnesota is now only about one-fifth of the 1931-1940 rate, and that neurosyphilis appears to have declined even more than syphilitic aortitis, possibly because of the more favorable influence of antibiotics. Especially noteworthy, moreover, was the fact that no instance of congenital syphilis was recorded in 2743 necropsies in children less than ten years of age during the years from 1949 to 1953.

Tonight I wish to review a series of necropsies performed by us over a period of twenty-five years, beginning in 1927, the year the University of Chicago Clinics opened. Over this period our necropsy rate has remained relatively unchanged (between 70-80 per cent) and the staff of pathologists has maintained a reasonable continuity with respect to necropsy procedures and terminology. Moreover, during this time the average age of our subjects has not changed remarkably. Thus the average age today is only about four years older than it was between 1927 and 1930. During the twenty-five years, also, our clinical services have been growing steadily, as has our necropsy service. In the meantime,

however, the character of our necropsy material has changed remarkably. For example, in the years between 1927 and 1940 much of our time at the necropsy table was taken up with problems of infection. Such diseases as lobar pneumonia, purulent meningitis, generalized fibrinopurulent peritonitis, puerperal sepsis and vegetative endocarditis were of practically daily occurrence and were often regarded as the principal cause of death. Since 1940, however, there has been a marked change both in the incidence and severity of these types of infection.

Although the principal emphasis in this discussion is placed upon chemotherapy and antibiotic treatment, it would obviously not be proper to ascribe all the pathologic alterations in infection to a single type of therapy, inasmuch as in the past twenty years infection rates for many diseases have been steadily coming down, and for a variety of reasons. These include improving standards of hygiene, medical education and hospital management, development of improved facilities for blood transfusions, including blood banks, better nutritional conditions and therapy, especially preoperative and postoperative, fluid and electrolyte management, improvements in diagnostic laboratories, etc. Nevertheless, the changes in the death rates from infection coincident with the widening use of chemotherapy and antibiotics have been too sudden to bring into serious question the tremendously beneficial effects of these therapeutic agents upon infections of many kinds. In short, too many hospitals for the treatment of contagious diseases have removed their isolation cubicles in recent years and gone into metabolic and geriatric work to make one doubt the effects of antibiosis.

In the material which I now wish to present I have charted the numbers of deaths attributed to a selected group of infectious processes per 500 consecutive necropsies in order to see what changes have taken place in our morgue service during these changing years. The diseases I have selected are: lobar pneumonia, purulent meningitis, generalized peritonitis, perforative appendicitis with generalized peritonitis, vegetative endocarditis and puerperal infection.

Lobar Pneumonia: For example, our first necropsy, performed in December of 1927, was of a patient who died of lobar pneumonia. From that time until 1940, in a series of 2000 consecutive necropsies, lobar pneumonia was considered to be the principal cause of death in fifty instances. Much of this was during a period when attention was focused upon pneumococcal typing and the administration of type-specific

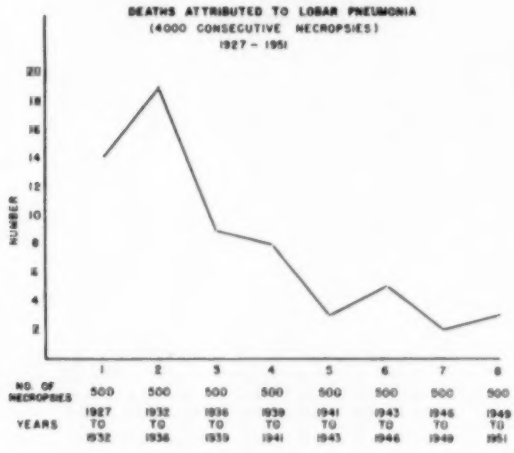

Chart I

serums (1932-1936). Sulfonamide therapy was not given, so far as I can ascertain until early in 1939, that is, to patients in this series. Since 1940, in a succeeding series of 2000 consecutive necropsies, the total number of deaths attributed to lobar pneumonia was only seven, and for the past few years we have had no cases at all. Our residents and medical students now learn about the pathologic aspects of lobar pneumonia only from books, from the reminiscences of older clinicians and pathologists, and from museum specimens. Chart I demonstrates our findings in terms of numbers of pathologic diagnoses of lobar pneumonia in each 500 consecutive necropsies, in a total of 4000 necropsies.

Purulent Meningitis: In the earlier years, when otitis media and mastoiditis were commonplace, deaths from meningitis were numerous on our service. Our third necropsy in 1927 was of an eighteen year old man with otitis media and a purulent meningitis, and in the ensuing 500 necropsies, thirteen deaths were attributed to this type of infection. From 1927 to 1941, in a total of 2000 necropsies, sixty-one deaths were ascribed to purulent meningitis. It should be noted, also, that our Department of Pediatrics was not established until 1930, so that the rise in the curve shown in Chart 2 is due largely to the growing service during the depression years. By 1939, sulfanilamide came into increasing use

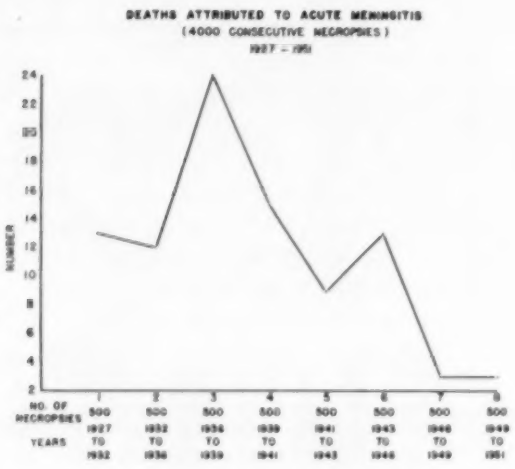

CHART 2

and soon we began to see a prolongation of survival time and the not infrequent appearance of localized meningitis and subdural abscesses. Since 1941, the fatality rate has declined steadily except for a slight rise in the years between 1943 and 1946, and in the past three years we have had only six deaths, one of these due to pseudomonas infection. It is apparent, therefore, that in our environment, where most of the meningeal infections are caused by antibiotic-sensitive strains of micro-organisms, deaths from purulent meningitis are no longer looked upon as one of the inevitable risks of childhood.

Acute Generalized Fibrinopurulent Peritonitis: In an active surgical service, and especially in one with a large volume of abdominal surgery, the hazard of generalized peritonitis is obviously ever present, regardless of surgical competency or of operating room efficiency. Our surgical service has grown steadily since 1927 so that, assuming an average competency of the surgeons and an average control of aseptic techniques, one might expect the incidence of generalized peritonitis to rise in proportion to the increase in operations. This was indeed the case during the years 1939 to 1941, due largely to local conditions in that it was in this period that more aggressive surgery for the treatment of malignancies was first intensively applied. It should be noted that of the forty-

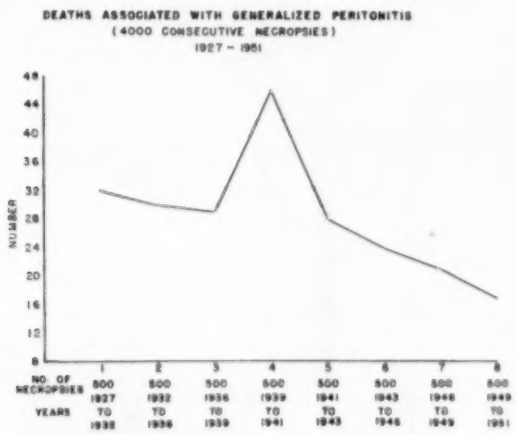

CHART 3

six instances of generalized peritonitis recorded at necropsy during this interval, approximately three-fourths were from the surgical services. Moreover, our blood bank was not functioning until September of 1942, at which time chemotherapy and antibiotic treatment were also increasingly utilized. At any rate, since 1941, the occurrence of postoperative generalized peritonitis has become rarer from year to year so that our surgeons are no longer greatly concerned about this formerly much-dreaded complication, even with the extensive one-stage operations now so generally done.

Deaths Attributed to Perforative Appendicitis: In connection with the problem of generalized peritonitis a question of considerable importance is the possible influence of antibiotic therapy upon the prevention of deaths from perforative appendicitis. Here our necropsy data are also interesting and suggestive. For example, during the period from 1927 to 1941, in a series of 2556 consecutive necropsies, death was attributed to perforative appendicitis and generalized peritonitis in seventeen instances. About one-half of the patients were over fifty years of age and none had received antibiotic therapy. In contrast, in the period from 1941 to 1952, in a series of 2434 consecutive necropsies, only two instances of perforative appendicitis and generalized peritonitis were recorded. One of these was in a two year old child and the other in a

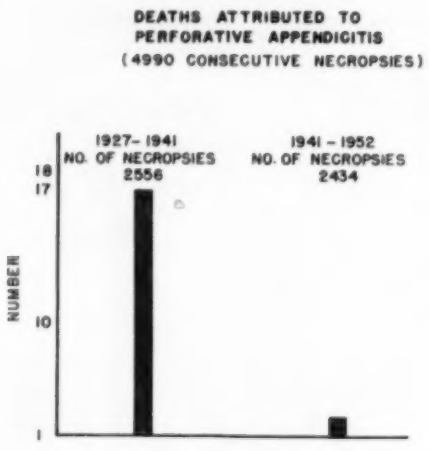

CHART 4

seventy-two year old diabetic, neither of whom received antibiotic treatment.

Comparable results have been reported in the surgical literature. For example, Hill and Butcher[11] analyzed the mortality rates from acute appendicitis for 2212 patients treated surgically in a general hospital in Kansas City, Missouri, between the years 1936 and 1950. Between the years 1936 and 1940, in a series of 738 patients, the mortality rate was 3.8 per cent. Between 1941 and 1945, in a series of 891 patients, and when sulfonamides were used, the mortality rate was 1 per cent. Finally, between 1946 and 1950, in a series of 583 patients, when sulfonamides, penicillin and streptomycin were used, the mortality rate was 0.5 per cent. Most of the deaths were due to peritonitis. The authors concluded that their figures furnish "another example of the change in the pattern of infectious disease brought about by the use of chemotherapy and antibiotics."

In a similar survey from the University of Virginia Hospital, Hawk, Becker and Lehman[12] compared a series of 1003 consecutive cases of acute appendicitis during the years 1943 to 1948 with an earlier series of 1069 cases observed between the years 1933 and 1937. Whereas in the earlier series the mortality rate was 3.27 per cent, the rate in the later series was 0.8 per cent.

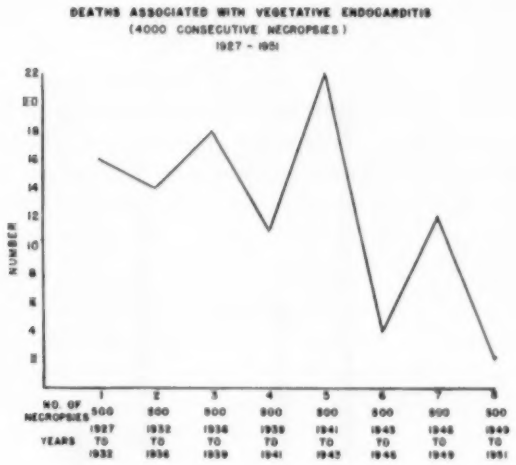

CHART 5

Vegetative Endocarditis: With the widespread use of chemotherapy and antibiotic treatment for respiratory infections and in relation to tooth extractions, one might expect to find evidence of an influence upon the incidence of acute vegetative endocarditis, particularly in view of the mounting clinical evidence of the beneficial effects of antibiotic therapy upon subacute bacterial endocarditis. An analysis of this problem from necropsy material offers some difficulties in that there may be considerable variability among pathologists in the recording of this diagnosis and in determining whether the lesion is terminal or of longer duration. With these limitations in mind, I have tabulated for the years under consideration the numbers of recorded instances of vegetative endocarditis for each 500 consecutive necropsies. In the first 2000 necropsies between the years 1927 and 1941 the total was fifty-nine; in the second 2000 necropsies the number was thirty-seven. If one compares the numbers for the first and the last 1000 necropsies, it becomes evident that only half as many were noted in the latter series. At any rate the curve of Chart 5 indicates a definite trend and so far as our data go, we feel that this lesion is also becoming more and more infrequent in our necropsy service.

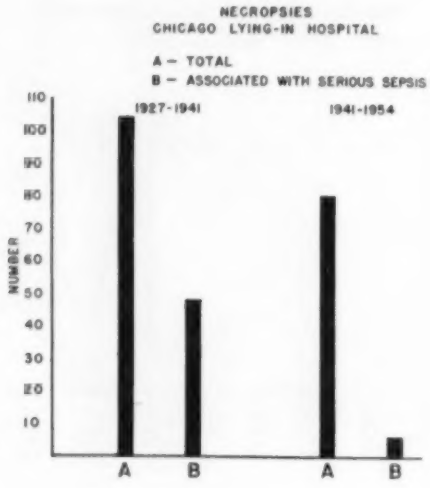

CHART 6

Obstetrical and Gynecological Infections: During the period under discussion we have performed all necropsies for the Chicago Lying-in Hospital, where, for many years, Dr. Joseph B. DeLee was a most fastidious exponent of scrupulous attention to asepsis. During this time he and many other obstetricians in this country were making progress in the reduction of maternal mortality, particularly since 1930. Nevertheless, between the years 1927 and 1941, in 104 necropsies performed by us in the Lying-in Hospital, serious infection was considered to be the dominant cause of death in forty-eight instances. This was usually puerperal sepsis, generalized peritonitis, suppurative meningitis and acute vegetative endocarditis. In our series the relative proportion of infection to non-infection cases continued near 50 per cent from year to year until about 1938-1939, during all of which time the necropsy permission rate was approximately 65 per cent.

In contrast, since 1941 we have performed eighty necropsies in this hospital and of these, only six have revealed dominating infection at the necropsy table. Although the necropsy rate has not changed appreciably during this time, the character of the patients has, in that the vast majority are now in older age groups and dying of malignancies or of

cardiovascular or toxemic complications. In short, the service has changed in type from obstetrical to gynecological. In the year 1952, for example, there was not a single maternal death from obstetrical causes.

Most of the data which I have presented were not influenced by the use of ACTH or cortisone. Although these therapeutic agents are now known to have a profound influence upon the inflammatory reaction, the evidence of their value in the treatment of acute infections has been disappointing and it seems to be rather generally believed that they do not act directly upon infective agents but rather as alterative agents upon the host. At any rate, a considerable amount of evidence is now available indicating their potentiality for reducing resistance to infection, for lowering antibody formation and as antianabolic agents. I refer particularly to the excellent review by Kass and Finland[13] and the monograph by Derbes and Weiss.[14]

Summary and Conclusions

These changing pathologic patterns of infection have become evident so recently that it is not to be wondered at that the incidental problems associated with the use of the chemotherapeutic and antibiotic agents seem at times to overshadow the significance of the overall accomplishments. Nevertheless, the special problems of antibiotic resistance of microbic strains, of superinfection, and of drug reactions should be constantly balanced against the facts of declining death rates and decreasing morbidity. This does not mean, of course, that these special problems should be treated lightly. When we recall, however, how quickly many of the problems relating to the toxic reactions of sulfonamide therapy were solved by clinical and chemical ingenuity, there is good cause for optimism with respect to the similar problems of drug reactions due to the antibiotics, as increasing attention is paid to such procedures as skin testing, oral administration, antihistaminics, better bacteriological controls, and changing focuses of use, all of which may in time help to reduce the incidence of complications. The man-made diseases will presumably be with us so long as chemists continue to manifest their remarkable resourcefulness in providing new compounds for clinical use. In the meantime pathologists will also have as one of their duties the study of the effects of these compounds upon living tissues. We can at least hope that these effects will continue to manifest

themselves mostly as minor problems and that we will have a decreasing concern about the major problems of lethal infections and postmortem lesions.

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THE NATURAL HISTORY OF STREPTOCOCCAL INFECTIONS*

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FROM time to time one must speculate on the nature of infections and the mechanisms by which these diseases are maintained in the population. The individual who indulges in such a pastime is indeed fortunate if adequate facilities and techniques are available to test various new theories and established concepts. During the past five years the staff** of the Streptococcal Disease Laboratory has had the opportunity to speculate and the facilities to test various ideas concerning the nature of streptococcal infections and their complications. Certain concepts and ideas had to be altered because of data obtained from these studies, and in their places many new theories were expressed. It is apparent that we are just beginning to understand the nature of streptococcal infections and their complications.

NATURAL HISTORY OF STREPTOCOCCAL INFECTIONS

Although all of the various groups of streptococci may infect man, most infections are caused by those organisms belonging to group A. Group A streptococci commonly invade the tissues of the upper respiratory tract, producing a disease which has been considered to be sufficiently distinctive so that it can be recognized in the majority of instances. Characteristically, the disease begins with the sudden onset of sore throat. Within a few hours the patient develops constitutional symptoms including fever, headache and malaise. The sore throat is

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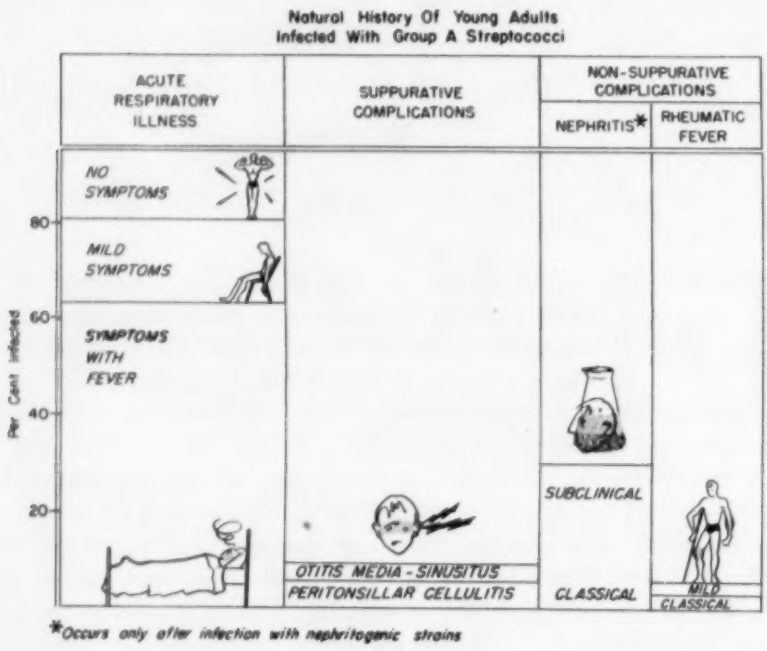

Fig. 1

usually severe, the patient experiencing considerable difficulty when swallowing solids or even liquids. Nausea and vomiting are prominent especially among children. Examination reveals a diffusely red oropharynx, although occasionally the mucous membranes may be pale. The tissues of the tonsils, oropharynx and soft palate appear swollen and edematous. Exudate, which may be pinpoint or discrete, is observed on the tonsils or pharynx in 60 to 80 per cent of the patients. The lymph nodes at the angles of the jaw are enlarged and, more importantly, are tender to palpation. The total leukocyte count is elevated and cultures usually reveal many hemolytic colonies of group A streptococci.

Although the above description characterizes the illness in the patient with a group A streptococcal infection, it does not indicate the total problem of such infections in man. Figure 1 presents the natural course of untreated streptococcal infections in young adult males. It is at once apparent that not all individuals infected with the group A streptococcus

develop symptoms. The majority develops fever and seeks medical attention. Approximately 20 per cent develop a sore throat which is not associated with constitutional symptoms of marked degree. A few develop no symptoms, but because of bacteriological and serological evidence, it is certain that they have been infected by the group A streptococcus. The exact proportion of such cases in relation to those with symptoms is unknown. Indeed, there is some evidence indicating that different strains of group A streptococci vary in their ability to produce symptoms. It is this feature of the natural history of streptococcal infections which makes effective control measures exceedingly difficult.

The acute symptoms of the respiratory infection persist for variable periods of time, but in general, in the uncomplicated case the symptoms are severe during the first twenty-four hours and by the fifth or sixth day the majority has recovered. During the acute illness and occasionally during the early phases of convalescence suppurative complications appear. Most common is the development of peritonsillar cellulitis. The frequency with which this complication and otitis media occur is determined by the presence or absence of tonsillar and adenoid tissue in the patient. Such complications are largely prevented if these lymphoid structures have been removed.[1] It is perhaps important to emphasize that peritonsillar cellulitis is not necessarily caused by the group A streptococcus itself, but rather the edema and infection of the tissues apparently predispose to this complication. Sinusitis is probably exceedingly common, but rarely are the symptoms severe enough to warrant a clinical diagnosis.

Of primary concern in the natural history of these infections is the development of the non-suppurative complications, acute glomerulonephritis and acute rheumatic fever. The importance of these complications is emphasized because the acute illness and the suppurative complications are readily controlled by proper antibacterial therapy, whereas the methods of treatment for the patient with nephritis or rheumatic fever cannot be said to be adequate.

Acute nephritis is a relatively uncommon complication of most group A streptococcal infections. For example, in a group of over 1,000 patients with infections caused by type 14 streptococci not a single instance of nephritis was encountered although each patient was observed for at least a three-week period.[2] Nephritis becomes important, however,

when the individual is infected with certain strains of group A streptococci. From the evidence presently available,[2-4] nephritogenic streptococci appear to be limited to the serological types 12 and 4, a new as yet unidentified type associated with scarlet fever, and perhaps type 25. In this country type 12 streptococci appear to be related etiologically to most cases of acute nephritis. Type 12 streptococcal epidemics may be followed by attack rates of classical acute nephritis varying from 5[5] to at least 13 per cent.[6] The number of patients who develop urinary signs of renal involvement without manifesting symptoms is even greater.[7] Once type 12 or type 4 streptococcal infections are introduced into large cities, the prevalence of nephritis may be maintained at high levels for several years. For example, in Honolulu an epidemic of nephritis began in 1950 and has continued at high levels for several years. Bacteriological and serological evidence indicates that this epidemic was caused by group A streptococcus, type 4.

One of the intriguing epidemiological problems in relation to acute nephritis which has not been adequately explained is the fact that the attack rate of nephritis following type 12 infections is variable. In epidemics presumably initiated by one strain of a single type of streptococcus multiple cases of acute nephritis may occur in some households, whereas in other families no nephritis develops following infection. Although such data would indicate that host factors might be responsible for the high attack rates of nephritis, there is little evidence to support such an hypothesis. It would appear likely that either naturally occurring variants arise which possess unusual nephritogenic capacities or some factor acts directly on the streptococcus producing such variants. The elucidation of the causes of such biological alterations in the streptococcus should assist in the study of the pathogenesis of nephritis.

Characteristically, the individual infected with type 12 streptococci excretes more red cells in the urine during the acute respiratory illness than individuals infected with other serological types. Furthermore, the patient who subsequently develops nephritis is especially likely to show moderate hematuria during the febrile stage of the streptococcal infection.[5] These observations might indicate that type 12 streptococci produce a substance which acts directly on the glomerulus. It is important to recognize, however, that the initial hematuria disappears and not until about ten days after the onset of the acute illness do symptoms of nephritis develop.

Once nephritis occurs, the physician should examine the urine of all individuals who have been in intimate contact with the patient. It is a common experience to observe inapparent examples of acute nephritis among those people who live in the same household with the index case. It is also advisable to obtain cultures of the oropharynx from all contacts and treat those individuals who are shown to be carriers of group A streptococci. Such therapy will prevent the spread of this organism to other individuals.

The majority of patients with acute nephritis recover within several weeks or months. Following complete recovery it is rare to observe a second attack of nephritis. This may be best explained by the observation that type specific immunity develops so that reinfection with a nephritogenic strain of streptococcus is unlikely.[3] It is for this reason that prophylaxis against streptococcal infections is *not* required in the patient who has recovered from acute nephritis.

In contrast to acute nephritis, acute rheumatic fever may develop following infection with any type of group A streptococcus. In general, the attack rate is 3 per cent, but it is considerably greater in those subjects who have experienced a preceding rheumatic attack. In addition, another 3 per cent of patients develop an illness characterized by mild symptoms or isolated physical or laboratory signs indicative of the rheumatic process. The abnormalities in the latter group disappear rapidly so that it is not possible to classify these complications as examples of rheumatic fever. However, from this group of patients may come those individuals who develop valvular heart disease in later years without giving a history of a preceding attack of acute rheumatic fever. Of the patients who develop classical attacks of acute rheumatic fever, many will subsequently exhibit signs of permanent valvular disease. Since this group of individuals is especially prone to recurrent rheumatic attacks, they must be protected from streptococcal infections. It is true that the patients develop immunity to reinfection with the same serological type of group A streptococcus that precipitated the attack of rheumatic fever, but infection with all other serological types is capable of producing a recurrence. Thus, the management of the rheumatic patient differs from the methods employed in the care of the patient with nephritis.

There are several factors that appear to be related to an increased attack rate for rheumatic fever following a streptococcal infection. These include an altered antibody response, a previous attack of rheumatic

fever and a positive familial history. Stetson[8] has demonstrated that there is a progressive rise in the attack rate for rheumatic fever as the magnitude of the antistreptolysin response increases. Investigation of this peculiar relationship has failed to elucidate its mechanism. By the use of several different antigens it was impossible to relate these observations to general immunological hyperreactivity of the host. Presumably, a greater antigenic stimulus is operative in the patient who develops rheumatic fever although there is no direct evidence to indicate that this is true.

That the individual who has experienced an attack of rheumatic fever is especially susceptible to a recurrence is well established. This increased susceptibility is evident for many years although the risk apparently decreases with time. Further studies of the nature of this increased susceptibility and the factors influencing it are urgently needed and may offer important clues as to the pathogenesis of this peculiar complication.

Finally, it has been assumed that some form of familial susceptibility to rheumatic fever is responsible for multiple cases occurring in single families. During the past four years the staff of the laboratory has been investigating this problem and has failed to substantiate this suggestion. All patients with streptococcal infections were interviewed and a history of rheumatic fever in the parents or siblings was recorded. The subsequent attack rate of rheumatic fever in patients with a positive family history was no different than that observed in patients with a negative family history.[8] It is therefore concluded that factors other than an inherited susceptibility to rheumatic fever are responsible for the occurrence of multiple cases in the family unit.

Maintenance of the Organism

The survival of the group A streptococcus as a human pathogen appears to be dependent on man himself. Although the organism may be isolated from various areas of the body under special circumstances, group A streptococci are most commonly found in the upper portion of the respiratory tract. From a limited experience it appears that streptococci usually gain access to the respiratory tract through the nasal passages.[9] Following an effective contact with a pathogenic strain the bacteria begin to grow in the tissues of the oropharynx. Although the incubation period is said to be one to three days, large numbers of group

A streptococci first make their appearance at about the time when symptoms develop. During the acute phase of illness numerous streptococci may be isolated from cultures of the oropharynx and anterior nasal mucous membranes. As the disease continues the number of group A streptococci decreases progressively, so that by the third or fourth week these organisms can no longer be isolated from cultures of the nasal mucous membranes unless the paranasal sinuses are acutely inflamed. Cultures of the tonsils and oropharyngeal lymphoid tissues now exhibit only a few colonies of streptococci on the blood agar plate. In contrast to common belief, the streptococci are not eliminated from the respiratory tract within three or four weeks. Indeed, if proper bacteriological techniques are employed, the majority of untreated patients will continue to harbor the infecting organism for at least four months.[10] The importance of the carrier state in relation to disease and maintenance of the organism is not well defined, but certain facts have been established and deserve emphasis.

Although the carrier state has not been considered injurious to the patient who has recovered from the acute streptococcal infection, recent evidence would indicate that the complication, rheumatic fever, does not occur unless the streptococcus continues to reside in the oropharynx. Thus, the elimination of group A streptococci by treatment with penicillin *after* the patient has recovered from the acute attack of pharyngitis will still prevent rheumatic fever.[11] Forms of therapy which do not eradicate the streptococcus fail to alter the attack rate of rheumatic fever. It is perhaps of some interest to note that only a few streptococci are required to initiate the rheumatic process.

The duration of the carrier state is also related to the development of streptococcal antibodies. Individuals who harbor only a few streptococci for a short period of time usually do not become ill nor do they develop antibody. For example, in one study of a food-borne outbreak thirty-one soldiers acquired type 5 streptococci without developing symptoms.[12] Of this group none of the individuals who carried the streptococcus for less than ten days developed antistreptolysin, whereas 77 per cent of those who carried the organism for longer periods showed an increase in antibody. Patients with streptococcal illnesses usually develop antibody, but early eradication of the organism with penicillin will inhibit 60 per cent of the antistreptolysin production.[13] Of more importance is the fact that type specific antibodies fail to develop under

similar circumstances.[14] This antibody develops slowly and preliminary data indicate that the individual who harbors the streptococcus for several weeks or months is especially likely to develop type specific antibodies.

There are two features of the carrier state which may play an important role in the maintenance of the organism. As stated previously, during the first three weeks following infection there is a rapid decrease in the number of streptococci harbored in the upper respiratory tract. Coincident with this decline, the ability to spread streptococci to other individuals is decreased. This fact has been demonstrated in the studies by Wannamaker[15] in which he also showed that individuals who harbor group A streptococci in the nasal passages are at least three times as dangerous as those subjects who carry streptococci in the oropharynx alone.

The second factor which may assume importance in the maintenance of the organism is biological alteration in the streptococcus as it is carried in the oropharyngeal tissues. Todd and Lancefield[16] and Watson, Rothbard and Swift[17] have shown that the infectivity of group A streptococcus is related to the presence or absence of M protein. As the carrier state progresses, many of the colonies of group A streptococci isolated from the respiratory tract lose their ability to produce M protein, and as a result they cannot be identified serologically as belonging to a specific type. By passage through mice, M protein production is reestablished and thereby the organism can be shown to be a variant of the original infecting strain. The studies of Watson[17] and Krause[18] have shown that streptococci isolated from carriers usually do not produce infection in monkeys when the strain employed contains no M protein. Presumably, therefore, carriers of strains of group A streptococci containing no M protein are not dangerous and are not important in the maintenance of the organism. It is possible that the decreased ability to spread observed in the carrier as time progresses is related not only to the decline in number of organisms but also to the gradual decrease in production of M protein.[19] Further studies are required before such relationships can be established.

The mechanisms by which the streptococcus is eliminated from the oropharynx of carriers are poorly understood. Wannamaker[15] has demonstrated that individuals exhibiting type specific antibodies are immune to infection by group A streptococci of the same serological type, but not to heterologous types. Presumably, therefore, recovery from the

acute illness is related to the development of type specific antibodies. It is possible that the initial decrease in the large number of streptococci growing in the oropharyngeal tissues is due to these specific antibodies. Since the carrier state is maintained after such antibodies develop, it is reasonable to believe that the streptococci are growing on and not in the tissues of the oropharynx. Only through such a mechanism can the carrier state be explained.

Finally, there has been considerable emphasis on the role of environmental reservoirs in the spread of disease and in the maintenance of the organism. Dust, blankets and clothing have been found to harbor group A streptococci in large numbers and therefore it has been assumed that these foci play a role in the spread of disease. The recent studies of Perry and his colleagues[20] confirmed the gross contamination of the environment by streptococcal carriers, but no evidence was obtained that such reservoirs are important in the spread of disease or in the maintenance of the organism as a pathogen of the respiratory tract. For example, the intranasal inoculation of naturally contaminated dust containing large numbers of typable group A streptococci failed to produce infection of the respiratory tract of man. Likewise, blankets contaminated by patients with streptococcal disease failed to increase the rate of infection in individuals who used such bedding when compared to individuals employing clean blankets. Such studies indicate that the streptococci in the environment are not important in the spread of respiratory disease, and, indeed, there is doubt as to whether they ever produce a respiratory infection.

In summary, although our knowledge of streptococcal infections is not complete, it is gradually becoming apparent that careful observation and study of the natural history of disease in man may lead to better methods of control. Furthermore, inquiry as to how the organism is maintained as a human pathogen should assist in the investigation of the pathogenesis of such important complications as rheumatic fever and acute glomerulonephritis.

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HYPERSPLENISM*

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SPLENIC enlargement is a common accompaniment of a host of infectious, non-infectious, and proliferative processes. In many of these some degree of anemia, leukopenia, or thrombocytopenia or all three together are found. Over the years the association of one or another of the blood cytopenias with splenomegaly has been termed, correctly or incorrectly, hypersplenism. It is the purpose of the present communication to define this term as accurately as possible within the bounds of our present relatively meager knowledge of splenic physiology and physiopathology.

HISTORICAL DEVELOPMENT OF THE CONCEPT OF HYPERSPLENISM

That the spleen was in some measure related to the blood did not become apparent until the era of histopathology was well advanced. In 1846, when Virchow,[1] the great German pathologist, described "Weisses Blut," he pointed to the very large size of the spleen and later used the term "Splenomyelogenous Leukemia"[2] for the condition. Apparently it was Gretsel[3] in 1866 who first used the term "Splenic Anemia" for cases in which there was both splenomegaly and anemia, thus implying that the anemia was splenic in origin. Banti[4] popularized the term in a long series of publications beginning 1882 and continuing for about thirty years. He concluded that the spleen was the site of a "noxa," which resulted in: 1) a low-grade febrile disturbance; 2) a certain degree of anemia and leukopenia; and eventually 3) cirrhosis of the liver. Although the nature of the "noxious" principle in the spleen was not defined, it was apparent from Banti's studies in these cases that a certain relationship was present between the spleen and the blood-forming apparatus. Banti's many descriptions of splenic anemia led eventually to the use of the term Banti's disease for almost all cases

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in which splenomegaly and leukopenia, with or without cirrhosis of the liver, were present. More recently, however, there has been an increasing tendency to restrict the use of the term to those cases of splenomegaly with leukopenia which simultaneously presented the various indications of cirrhosis of the liver. Banti's idea of a "noxa" originating in the spleen and terminating as cirrhosis of the liver was eventually largely discarded when it was found that cirrhosis of the liver was in all probability the initiating factor of the splenomegaly by way of portal hypertension and that the leukopenia was a later phenomenon.*

Eppinger, whose writings on spleen-liver relationships were perhaps also ahead of their time, discussed the possibility in 1916 of "Aktiven Milztumor," i.e., of splenomegaly of an "active" type resulting in changes either in the white cells directly or in their relationship to the liver. In his textbook, "Hepato-Lienalen Krankheiten,"[5] Eppinger described several cases with enlargement of the spleen and various forms of cytopenia. At about the same time, Frank,[6] working in Germany, described cases with splenomegaly in association with leukopenia or thrombocytopenia and concluded that a definite relationship probably existed between an enlarged spleen and the bone marrow, the end-result being either a lowered white count or a lowered platelet level. Who first used the term "hypersplenism" is not accurately known, but it began to appear in Chauffard's writings from 1907 on[7] and subsequently, and in those of Morawitz[8] and Eppinger[5] at a later date. In 1939, Wiseman and Doan[9] described "Splenic Neutropenia," a condition which they characterized as presenting splenomegaly, marked leukopenia with neutropenia, frequent infections, and a favorable response to splenectomy. Dameshek[10] in 1941, and subsequently, indicated that hypersplenism might be either "selective" or "total"; i.e., that the splenomegaly might be associated either with anemia or leukopenia, or thrombocytopenia, or with combinations of these cytopenias. He also pointed out that "primary" and

* Banti was in many respects far ahead of his time. His first description of "Splenic Anemia" was made in 1882 at the age of thirty. He defined splenic anemia as a progressive idiopathic anemia, accompanied by idiopathic non-leukemic hypertrophy of the spleen with variable enlargement of the liver. His thinking on the subject may be summarized in the following quotation from that work (freely translated):

"The hypotheses that may be formulated are principally two: 1) that the spleen destroys large numbers of red cells; 2) that certain biochemical processes taking place in the spleen result in the development of abnormal metabolites which enter the circulation and have secondary effects on hematopoietic organs."

Even at that early date, Banti was a strong proponent of splenectomy. Later, in 1910 et seq., he performed crucial experiments in the production of hemolytic anemia by hetero-antibodies, pointed to the central importance of the spleen in hemolytic anemia, and continued his advocacy, with Michell, of the operation of splenectomy for various blood cytopenias. It was largely through his insistence that the first planned splenectomies in the so-called blood dyscrasias were performed. The success of splenectomy in certain cases of hemolytic anemia led Kaznelson to suggest this operation in idiopathic thrombocytopenic purpura.

"secondary" forms might be present; that is, that hypersplenism could be either a primary disturbance of the spleen and of unknown origin, or that in the presence of splenomegaly due to some well-defined cause such as tuberculosis, sarcoid, etc., these various cytopenias might develop. Later, in 1946, Doan and Wright[11] described splenic "panhematopenia" or, as we term it, "pancytopenia." Doan and his group have concluded that the various types of cytopenias were due to selective sequestration of the various hematologic elements in the enlarged spleen and in their eventual phagocytosis.

Our own concept is that the enlarged spleen has an indirect or humoral action upon the bone marrow, either by preventing the growth or maturation of the various cells, or else by blocking their delivery from the marrow to the blood. That *selective* sequestration and phagocytosis occur has been denied by Dameshek and his group,[12] although they have conceded that in certain cases of hypersplenism with increased hemolysis, such a possibility may well be present. These divergent theories of hypersplenism, neither of them well founded on experimental evidence, have been under discussion for a number of years, and will be further discussed below. At this point, however, since hypersplenism is to be discussed, one may ask whether there are any indications of normal functional activity of the spleen, or "splenism."

Splenism

The spleen, although it may be removed with impunity from the normal individual without any apparent decrease in his well-being or general health, nevertheless appears to have a number of rather well-defined functions. The "reservoir" function of the spleen was pointed out by the British physiologist, Barcroft,[13] in a series of experiments using the cat. The spleen was exteriorized and its size noted following such procedures as hemorrhage, excitement and the like. These experiments, as well as others in which blood volume was measured, demonstrated conclusively that the size of the spleen fluctuated widely during the day and in response to specific "emergency" situations. With excitement and hemorrhage, a definite diminution in the volume of the spleen took place, indicating that a certain amount of blood was thrown into the general circulation by the contracting spleen. In other words, the body appeared to possess a mechanism for "auto"-transfusion which might be of value under such emergencies as acute blood loss, etc. Later,

Knisely[14] demonstrated by studying the surface of the living spleen of the intact animal with the cold quartz light that the sinusoids of the spleen were at times empty, at times full. Blood might "stagnate" in closed sinusoids for hours at a time (erythrostasis). This process, which could be likened to the incubation of blood in a warm test-tube, might conceivably result in modifications in the structure of the red blood cells including such changes as increased thickness, eventually leading to metabolic changes as well.

In addition to these mechanical functions, the spleen may also be thought of as a very large lymph node, or as a lymphoid filter, poised between an artery and a vein. The ordinary lymph node is situated between lymphatic channels, but in this unusual "lymph node," the organ is situated between a large artery, (the splenic artery), the largest branch of the celiac axis, and a large vein, (the splenic vein), the largest tributary in the portal vein. The large amount of blood going in and out of the spleen suggests its importance to the human economy.

The large collection of lymphoid tissue within the spleen indicates that it participates in the various functions of the lymphoid cells, although these are not too well known. The lymphocytes are probably concerned with combating infection with the production of antibodies. Undoubtedly, they have many other functions, including participation in fat and protein metabolism. The spleen is furthermore the largest single collection of reticuloendothelial cells in the body and as such must participate in the various functions of these phagocytic cells. The reticular and endothelial cells of the spleen have been known for years to be concerned with antibody production, perhaps in connection with their role as scavenger cells for red cell fragments, leukocytes, platelets and various other materials which must be destroyed before their end-products can enter the blood stream. In acute infections, the reticulo-endothelial cells may be said to participate as a "second line of defense." During many subacute infections, they become greatly increased and the entire reticuloendothelial system hypertrophied, thus accounting for the frequent splenomegaly under such circumstances. (Cf. typhoid fever, malaria, kala-azar, etc.)

Spleen an Endocrine Organ?

Of particular interest is the question as to whether or not the spleen is an endocrine organ. Although no definite statement regarding this can

be made at this time, there are many bits of evidence pointing in that direction. The literature to 1933 has been amply documented by Lauda.[15] Very little change has taken place since then with the exception of the relatively recent studies of spleen-adrenal cortical relationships.

A classical method for studying the endocrine function of an organ is to remove it and study the effects developing thereafter. Thus, thyroidectomy, adrenalectomy, and hypophysectomy have been studied extensively, and their effects noted. Various well-defined changes develop which can be traced to the deficiency or lack of hormonal factors derived from the organ removed. Similarly when splenectomy is performed a number of changes develop,[10] most of them detectable by rather subtle means such as blood counts and careful examination of hematologic changes. Thus, when the spleen is removed, there is a slight though definite increase in red cells, a well-defined increase in white cells, usually with a doubling of the white cell count, and a marked increase in the platelet level with usually a doubling or tripling of the original count. These changes might indicate either that the spleen, now missing from the body, did not destroy the various blood cells manufactured in the bone marrow or was not present in an inhibitory capacity to reduce or regulate the blood cells derived from the bone marrow. However, at least two other changes develop, one being the presence of Howell-Jolly bodies, and the second, the development of a relatively thin red cell population characterized by the presence of leptocytes or target cells.[10]

The Howell-Jolly body is a small fragment of nuclear material which is occasionally noted within the cytoplasm of the mature red cell. At times seen in severe blood dyscrasias, it is a constant phenomenon following splenectomy and is found in approximately 1 per cent of the red cells. Normally, the mature red cell in the circulation is completely devoid of nuclear material. That small fragments of nuclei may be retained in the relatively new red cells as they are produced from the bone marrow following splenectomy indicates that there is incomplete denucleation of the red blood cell in the absence of the spleen. This might indicate that the normal spleen has a remote effect on the marrow with respect to the final stop of complete denucleation of the red cell. Using the technique of parabiosis, in which two animals are joined, both Hirschfeld[16] and Lauda[15] showed that the appearance of Howell-Jolly bodies was controlled by a probably humoral factor

derived from the spleen. The removal of one spleen of a parabiotic pair of animals caused no modification of blood counts and no Howell-Jolly bodies were found. However, if both spleens were removed, Howell-Jolly bodies developed in the red cells of both partners. Similar observations were made in the case of bartonellosis, a peculiar bacterial infection which is present in many strains of splenectomized rats. The infection is not detected in the intact rat, nor in a parabiotic pair of rats if the spleen is removed from one partner. However, if the spleen is removed from both, bartonellosis develops in both, and the animals die of acute hemolytic anemia. These experiments, although by no means conclusive, indicate that the spleen is concerned in the ultimate denucleation of the normoblast of the bone marrow as well as with the tendency to keep Bartonella infection latent in the rat harboring this bacterium. These experiments do not rule out the possibility, however, that the spleen removes particulate matter from the red cell; thus, it is possible that the final remnant of the normoblastic nucleus or of the Bartonella bacterium within a red cell is removed by the spleen normally, while in the absence of the spleen these abnormal bodies are retained.

More recent experiments point to the possibility that the spleen, the bone marrow, and the adrenal cortex are related through their hormones. Thus, the adrenal cortical hormones, cortisone and hydrocortisone, have well-defined effects on the lymphoid tissue, spleen and the thymus.[17] Following repeated administration of these hormones, there is a well-defined reduction in the weight of these tissues, due either to actual lysis of the lymphoid tissues, or to some other mechanism inhibiting lymphocyte production. Thus, it may be said that the adrenal cortex, through its hormone cortisone exerts an inhibitory effect upon lymphoid, thymic and splenic tissues. Conversely, there is some evidence, although not as clearcut, that the same hormones exert a stimulatory effect on the bone marrow, thus resulting in a well-defined increase in reticulocytes, erythrocytes, polymorphonuclear cells and blood platelets, all the elements in other words derived from the bone marrow. From these experiments, one may postulate a reciprocal effect between the lymphoid tissues, including the spleen and the thymus, and the bone marrow, at least in their relationship to cortisone. Such a reciprocal relationship has been discussed for many years and is well brought out in the acute infections. If it is postulated that the adrenal cortex has an inhibitory effect on the spleen and simultaneously a stimulating effect

on the bone marrow, a third angle of a hypothetical triangular "axis" can be built by assuming that the spleen has an inhibitory effect on the bone marrow.[18] This inhibitory effect is disclosed, as pointed out above, in the experiments with splenectomy which demonstrate a well-defined leukocytosis and thrombocytosis. It is brought out very strikingly by either hemorrhage or acute hemolysis in the splenectomized individual. Here, a very striking increase takes place in early red cells and white cells, with many nucleated red cells and myelocytes. These various features seem to indicate a regulatory function of the spleen upon the bone marrow.

In recent years some further, perhaps more direct evidence has been obtained indicating that the spleen is actually an endocrine organ with distant effects on other tissues. Ungar has extracted from the spleen two mutually antagonistic materials, splenine "A" and splenine "B". According to this worker, splenine "A" has an effect on the blood vessel wall, increasing its resistance, and splenine "B" an antagonistic effect on the bone marrow megakaryocytes, with the production of thrombocytopenia and thus the possibility of hemorrhage. In more recent experiments, Ungar[19] has demonstrated that splenine "A" is concerned with anti-fibrinolytic mechanisms and that splenine "B" may accelerate fibrinolysis; in other words, opposing activities.

Probably more definitive are the experiments of L. O. Jacobson[20] on spleen shielding which indicate a well-defined relationship between the spleen and the bone marrow. In these experiments, when rats were given a uniform large dose of x-ray, marked cytopenias developed as a result of bone marrow aplasia and all the animals died. However, when the spleens of another batch of animals were exteriorized and shielded from the effects of x-ray by a suitable lead covering, and the animals then given the same large dosage of x-ray, the cytopenias that developed were slight, and the mortality of the animals was low. With the exception that the spleen was shielded from the effects of x-ray, the conditions of the experiment were identical. The results of these experiments indicated that the spleen might contain a factor which protected the bone marrow against cytopenic effects of x-radiation. Further experiments tended to confirm this hypothesis. Thus, when the animals were given the same dosage of x-radiation without spleen shielding and either simultaneously or shortly thereafter a small transplant of splenic tissue was introduced into the abdomen, again the animals were protected from

the effects of x-ray. In further experiments, extracts were made from the spleen and cell-free material was injected into the animal either just before the x-ray exposure was given, or shortly thereafter, and again the cytopenias were slight and the mortality low. These and various other experiments indicated that lead shielding of the spleen prevented injury to the bone marrow and that a protective material was present in the spleen. Although not completely proved, all indications are present that the substance in the spleen is of humoral nature, which by its introduction into the circulation has remote (and protective) effects on the bone marrow.

In another series of experiments, suggestive evidence was obtained that a splenic hormone elaborated by the spleen might have a regulatory or cytopenic function on the leukocytes of the bone marrow. Thus, Palmer, Cartwright et al.[21] showed that splenectomy resulted in a doubling of the leukocyte count in rats. When only portions of the spleen were removed, no rise in leukocytes took place unless less than 10 per cent of the spleen was left intact. At this point, there was again an approximate doubling of the leukocyte count, as with total splenectomy. The leukocytic effect of splenectomy could be abolished by introducing into the peritoneal cavity a small transplant of spleen of approximately 10 per cent of the normal spleen in size. The transplant could be either "auto" or "iso" in type. It was concluded from these experiments that the spleen probably contained a hormonal or humoral factor which prevented the white count from rising or at least had some regulatory effect on the bone marrow leukocytic tissue, thus keeping the leukocyte count at normal values. In further experiments by the same group,[22] it was demonstrated that a hypersplenic effect could be produced by transplanting one or more spleens into the peritoneal cavity of the intact normal rat.

These and other experiments suggest that the spleen may have an effect on the bone marrow through some remote and as yet poorly-understood mechanism. If this is correct, the assumption must therefore be made that hormonal or humoral factors released by the spleen have an effect on bone marrow cells. The proof of this hypothesis is not yet at hand, since work with splenic extracts has thus far been inconsistent. Although splenic extracts have been prepared by a number of observers and injected in animals, the changes produced, whether on blood or other tissues, have been quite inconsistent, and in fact often-

times negative. This is quite in contrast with the positive results so readily obtained with extracts of thyroid or adrenal glands, and brings the matter of splenic hormones seriously to question. There is nevertheless the possibility that effective extracts of spleen have yet to be prepared.

Hypersplenism

The concept of *hypersplenism* must be approached with a certain degree of caution since it is not definitely known whether "splenism" or "eusplenism" exists. Nevertheless, the concept has been a very useful one clinically and has tended to advance our thinking regarding the relationship of the spleen to the bone marrow and the blood cells, as well as to the practical merits of splenectomy in a given situation. What then is our concept of hypersplenism? As already stated, we have the relatively simple belief that hypersplenism is a condition in which the equivalent of two, three or more spleens (splenomegaly) is present and that this results in an unusually marked degree of inhibitory or depressant effect on the bone marrow. The greater the increase in splenic tissue, the greater, usually, is the degree of hypersplenism. Anatomic enlargement of the spleen is, we believe, productive in some obscure manner of physiologic hyperfunction. Thus, various conditions associated with splenomegaly are usually (not always) accompanied by neutropenia, anemia, or thrombocytopenia, or by a combination of these, including pancytopenia. The "proliferative" splenomegalies—polycythemia, leukemia, etc.—are, however, usually associated with leukocytosis. One or more cytopenias may be expected with almost any type of splenomegaly. Thus, a cytopenia with splenomegaly does not necessarily point to any specific diagnosis but merely to the fact that splenomegaly is present and with it the resultant physiologic or physiopathologic effects of the enlargement of this organ with its remote effects on the bone marrow. Hypersplenism can be further defined as showing the following features: 1) splenomegaly; 2) blood cytopenia or cytopenias; 3) a "full" marrow, i.e., a normally hypercellular marrow, free from proliferating cells. The full marrow may further show either maturation arrest of the affected cell type, or a normal appearance. The latter may be interpreted as "blocked delivery." An all-important fourth feature of hypersplenism is that splenectomy will result in the correction in the cytopenia or cytopenias; if it does not, and all the

other features are present, they can be discounted because "the proof of the pudding is in the eating."

Hypersplenism occurs in a variety of conditions with splenic enlargement. These may be listed as follows: 1) subacute and chronic infectious hyperplasia of the spleen; 2) portal hypertension, including cases with cirrhosis of the liver as the primary feature or those in which there is thrombosis of various parts of the portal circulation, or thrombosis of the splenic vein alone; 3) lipid cellular diseases, more particularly Gaucher's disease, in which the normal splenic tissue is almost completely occupied by lipid material stored principally in the reticuloendothelial cells in the spleen; 4) certain cases of lymphosarcoma, primary in the spleen; 5) other neoplasms including such relatively benign ones as hamartoma and splenic cyst; and finally, 6) conditions in which the spleen is enlarged and yet shows no particular disturbance; these are ordinarily classified as non-specific and might conceivably be the end result of a previous infection involving the spleen.

Hypersplenic syndromes may possibly induce a variety of effects, but the only ones that can be recognized at present have to do with the blood cells. Thus, hypersplenism may be associated with either neutropenia, thrombocytopenia, or anemia or with various combinations of these three. Furthermore, the hypersplenism may be "idiopathic" or "primary," or it may be secondary to some well-defined cause. Although the term "idiopathic" is unfortunate, its use must nevertheless be continued, since the cause for many cases of splenomegaly is still obscure. In the presence of the blood cytopenias, the bone marrow is characteristically "full" and usually hyperplastic. The cell type that is reduced in the blood is usually increased in the bone marrow. Thus with splenic neutropenia, there is usually a granulocytic hyperplasia in the marrow, and with splenic thrombocytopenia, the marrow megakaryocytes are usually increased. To a certain extent, this holds true for the occasional cases of splenic anemia due apparently to an inhibitory factor.

Although hypersplenism, as we have defined it, undoubtedly exists, there is no certainty that the "inhibitory" concept of its nature is the correct one. Doan and his group[23] have emphasized the phagocytic thesis to explain the various cytopenias, which they believe are due to selective sequestration and phagocytosis by the abnormal spleen. As evidence for this concept, Doan and his group point to the results of the adrenalin test. In this test, a small amount of adrenalin is injected subcutaneously

and blood counts are obtained before and after. In a positive test, the cell type low in the blood becomes definitely increased, indicating "selective sequestration" in the spleen. Our own observations with this test have been either completely negative, or if not negative, very questionable and often confusing.[24] Furthermore, following splenectomy in such cases, the post-adrenalin results have either been similar or even more striking than previously, thus indicating that adrenalin might simply result in a redistribution of cells from various tissues or organs into the blood stream and that the leukocytosis or other cellular increase might have little or no relationship to selective sequestration within the spleen. Another point emphasized by Doan and his group[25] is that counts obtained at operation from splenic arterial blood contain much larger concentrations of the cell type reduced in the blood than counts from the splenic venous blood, thus indicating that the spleen sequesters the cells coming into it by way of the artery. Again, however, our own results have failed to confirm these observations.[26] In our experiments, unusual care was taken to reduce agglutination and coagulation effects by the use of plastic tubing and siliconized apparatus. By these techniques, no significant alterations were demonstrated between blood counts obtained from the splenic artery and vein. Doan and his group also point to supravital studies of splenectomized material which show definite sequestration of the various cellular elements.[23] Curiously enough, fixed tissue sections of the same organ in the same condition usually show little or no evidence of sequestration or phagocytosis, and in our studies such evidence has ordinarily been lacking, except in certain cases of hemolytic anemia.

Our conclusions that hypersplenism is due to an inhibitory phenomenon induced in some manner by a large spleen mediated through a humoral mechanism, are based chiefly on bone marrow observations both before and after splenectomy. Particularly in the case of the megakaryocytes and thrombocytopenia, and to lesser extent, in the case of the granulocytic series with neutropenia, there is often evident a well-defined maturation arrest before operation, not present after operation. Proof of an inhibitory mechanism would be clearly provided by the preparation of splenic extracts, which when injected, would cause identical effects in animals. Unfortunately, such proof has until now been lacking, at least in any consistent degree, although we are now actively engaged in re-studying this problem with lyophilized extracts of spleen.

The *diagnosis* of hypersplenism is made on the features that we have already emphasized. These include: 1) The findings in history and physical examination of well-defined splenomegaly, the spleen being enlarged usually at least two to three fingersbreadth below the left costal margin. Many cases with hypersplenism show such features as vague aches and pains in the joints, with or without actual joint changes. Those with thrombocytopenia may show ecchymoses and petechiae. In general, however, the outstanding feature of a case of hypersplenism is the presence of a well-defined splenomegaly. 2) The blood changes; there are anemia and/or leukopenia with neutropenia, and/or thrombocytopenia, or a combination of these findings. 3) The marrow findings, which reveal a normally cellular or hypercellular preparation in which are present normal or increased numbers of nucleated red cells, normal or increased numbers of granulocytes, and normal or increased numbers of megakaryocytes. In the case of neutropenia, the granulocytes in the bone marrow are greatly increased, often at the expense of the nucleated red cells or the megakaryocytes; whereas in the case of splenic anemia, the nucleated red cells are increased and in thrombocytopenia there is usually a marked increase in megakaryocytes. In most instances, particularly in the case of the neutropenic and thrombocytopenic states, there is simultaneously some degree of maturation arrest of the affected cell series. Thus, with neutropenia, granulocyte maturation may proceed to the level of the myelocytes, the young metamyelocytes or the band-form myelocyte according to the case at hand. Mature polymorphonuclear cells are frequently conspicuous by their absence. In the thrombocytopenic situations, the megakaryocytes often show greatly diminished platelet production. In many cases, however, no evidence of maturation arrest is present, but the marrow shows the presence of normal or increased numbers of the cell type or types deficient in the circulating blood. It should be emphasized that the "full" bone marrow commonly found shows no evidence of the marked degree of primitivity of the leukocytes seen in leukemia, but the granulocytes are all of the normal mature or semi-mature variety with relatively few myeloblasts. It must be stated, however, that occasional cases of "aleukemic" leukemia may mimic hypersplenism very closely. Although in such cases a relatively large number of primitive cells is usually seen, we have observed others in which the leukemic nature of the condition became apparent only after splenectomy.

A diagnostic test that we have utilized more and more in recent years and that is particularly useful in the differential diagnosis of aleukemic leukemia from hypersplenism, is splenic puncture.[27] This is performed by the use of a 20 or 21 gauge needle, affixed to a 5 cc. syringe which is plunged very quickly into the body of the spleen as it extends below the costal margin, and as the patient holds his breath in inspiration. The entire maneuver takes a few seconds. A very small amount of splenic material, no more than 0.2 or 0.3 cc. is aspirated and quickly spread on a few glass slides. There is usually sufficient material to allow one to make the diagnosis between a normal cellular picture or that due to leukemia, myeloid metaplasia, or lympho- or reticulum cell sarcoma. Primary lymphosarcoma of the spleen may simulate hypersplenism quite closely and, in fact, may be associated with that disturbance. In the early stages, the bone marrow may show no infiltration with abnormal or primitive lymphocytes. This negative finding, in association with the splenomegaly, and the cytopenias, may lead to the diagnosis of primary hypersplenism. Lymphosarcoma should be kept in mind, however, particularly when there is any evidence of fever, night sweats, or other systemic manifestations, or when the sedimentation rate is considerably elevated. The diagnosis of lymphosarcoma can usually either be established or ruled out from the results of the splenic puncture. With lymphosarcoma or reticulum cell sarcoma, very large numbers of primitive cells with abundant nucleoli are readily evident in most instances. In some cases, the lack of "topography" as obtained with open biopsy sections, may make the diagnosis difficult, and the diagnosis may only be made by open biopsy or splenectomy. It is often wise, even in a case which seems to be quite typical for "primary" splenic neutropenia, to have the negative results from a splenic puncture before final resort to splenectomy is made.

Splenic Neutropenia

In considering more specifically the different types of hypersplenism, *splenic neutropenia* will be first discussed since in many respects it is the most clearcut of the hypersplenic syndromes. In this condition, the presenting symptom is often that of recurrent infections, at times very severe. During a period of years, there are frequent bouts of fever accompanied with sore throat, sores of the mouth, and possibly infected lesions of the hands and feet. Finally, a blood count demonstrates the

well-defined leukopenia and neutropenia. In cases due to hypersplenism, the spleen is ordinarily enlarged two to six centimeters below the left costal margin. There is usually little, if any, lymphadenopathy, and the remainder of the physical examination is ordinarily negative with the exception of ulcerative lesions of the gums and mucous membrane of the mouth and pharynx, which are present during the acute episodes. The cytopenia is usually quite selective for the granulocytic series, but a slight degree of anemia and thrombocytopenia may be present. The leukocyte count may fluctuate considerably, but in a typical case, it varies between 1,000 to 3,000 per cmm. with granulocytes from 0 to 20 per cent.

The cause for the splenomegaly and its associated cytopenias may not be apparent in most instances; however, in some cases there are definite indications of a primary disease. Such primary or fundamental conditions include rheumatoid arthritis, portal hypertension and cirrhosis of the liver, Gaucher's disease, sarcoidosis, brucellosis, chronic malarial splenomegaly, chronic syphilis and chronic tuberculosis. In undiagnosed splenomegaly with neutropenia, since the latter is non-specific, every attempt should be made to rule the presence of these various conditions in or out by appropriate clinical and laboratory studies. Some of these must be searched for by specific techniques, including, in a suspicious case of sarcoid, the removal of some tissue from above the clavicle in the region of the scalenus anticus muscle. Rheumatoid arthritis should be considered in every instance since the Felty syndrome may simulate so-called primary splenic neutropenia very closely and conversely the latter condition may be simply a variant of rheumatoid arthritis in which the joint manifestations are relatively mild. Finally, disseminated lupus may masquerade as splenomegaly with neutropenia and therefore in every case of suspected hypersplenism, the L.E. test should be performed.

Splenectomy should be considered in every case of splenic neutropenia when both the splenomegaly and the neutropenia are sufficiently severe, the neutropenia being marked enough to have resulted in frequent bouts of infection. The operation should be performed only after lymphosarcoma, disseminated lupus, syphilis, and malaria have all been adequately ruled out. One should also know the status of the liver function and whether or not sarcoid is conceivably present. It is thus safer to consider that every splenomegaly has a well-defined cause, which

should be ascertained by all possible means. Even with all these safeguards and unusually careful studies of the marrow, splenectomy may uncover a completely occult leukemia or sarcoma, or at the time of operation, a liver biopsy may demonstrate cirrhosis. It should be noted, however, that if well-defined cytopenias are present, splenectomy will almost always be followed in all of these entities (whether rheumatoid arthritis, lymphosarcoma, or cirrhosis of the liver) by well-defined increases in granulocytes and leukocytes. The rise in the total or absolute number of granulocytes is usually to normal or low-normal values (3,500 to 5,000 granulocytes), in the presence of a slight leukocytosis of 10 to 12,000. There is thus usually a well-defined lymphocytosis of 40 to 60 per cent following splenectomy; this should occasion no particular comment and is a common finding in normal individuals after splenectomy as well.

The term "splenic anemia," popularized by Banti, is used relatively little at the present time, although it might reasonably be used far more. Two main types may be discriminated, one hemolytic, the other non-hemolytic. In the hemolytic type ("hypersplenic hemolytic anemia") all the various features of a hemolytic process are present, including anemia, slight icterus, bilirubinemia, and a well-defined increase in reticulocytes of 3 to 10 per cent. There is simultaneously leukopenia and thrombocytopenia. The Coombs test is negative and no abnormal antibodies can be detected in the serum. The fecal urobilinogen content is high. Bone marrow examination reveals a markedly hypercellular preparation in which the nucleated red cells are conspicuous by their marked increase, but there are also increases in granulocytes and megakaryocytes. Splenectomy is followed by a striking and permanent increase in the blood counts to normal values. In some of the cases, the sections of the spleen show, in addition to congestion of the pulp, a well-defined erythrophagocytosis, indicating that the anemia is due at least partly to phagocytosis of the red cell elements in the spleen.

As for the non-hemolytic types of splenic anemia, these are generally associated with more fundamental disturbances, involving cirrhosis of the liver, Gaucher's disease, and possibly rheumatoid arthritis. Since there is no evidence of increased hemolysis in these cases, it is distinctly possible that the anemia is on the basis of splenic inhibition of the red cell elements in the bone marrow. Splenic pancytopenia, like splenic neutropenia, occurs in a variety of conditions, although in some cases it is

"idiopathic" and the splenic sections show non-specific hyperplasia. It should be noted that a fairly common cause for pancytopenia is sarcoid of the spleen, and that splenomegaly may be the only objective manifestation of that disorder.

Some note should be taken of Banti's syndrome, which is often used synonymously with congestive splenomegaly, although in Banti's original descriptions, he believed it was a "primary" condition of the spleen, with that organ producing a "noxa" which injured both the liver and the bone marrow. This concept that the spleen injures the liver has been well-nigh discarded, and it seems certain that most of Banti's cases were examples of cirrhosis of the liver with secondary portal hypertension and splenomegaly, and with ultimate leukopenia and neutropenia. In later years, Banti's disease was used to designate almost any splenomegaly with cytopenia, but as the diversity of the splenic histology became evident, it was realized that the cytopenias were simply the pathophysiologic end-products of an anatomical disturbance, i.e., the splenomegaly. If one still wishes to use the term Banti's syndrome, it should probably be reserved for those cases showing 1) chronic hepatitis associated with some degree of hepatic failure; 2) portal hypertension; 3) splenomegaly; and 4) the various hypersplenic effects of anemia, leukopenia, neutropenia, and thrombocytopenia. It is well to remember that splenectomy in these cases is followed by an improvement in the hypersplenic effects only, namely by increases in the white cells, granulocytes and platelets, and to some extent in the red cell count. There is usually little if any effect on the portal hypertension and certainly none whatever on the degree of hepatic failure. On the other hand, simple splenectomy may be followed by long-sustained improvement in the tendency to bleed from varices. This is perhaps due to such features as the reduction of blood in the portal circuit following splenectomy, and to a rise in the platelet count to normal or high values. For example, in one of our cases of juvenile cirrhosis with hematemesis, splenectomy was followed by a cessation of bleeding and a well-defined increase in red cells, white cells and platelets persisting for eight years after operation. Following another hematemesis, a portocaval shunt was performed, and the patient died within a week after operation. In another case well-marked anemia, neutropenia and thrombocytopenia were all relieved very dramatically by splenectomy and spleen-renal shunt. Unfortunately, however, the degree of hepatic failure became consistently and rapidly worse, and

the patient died about six months following operation.

In every instance in which the Banti syndrome is thought to be present, a consideration of simple splenectomy versus the spleen-renal or the portocaval shunt should be discussed and the limitations of each maneuver should be stressed. Splenectomy relieves the hypersplenism and is a relatively simple operation. The shunt operations are physiologically superior for their effects on portal hypertension. They are, however, much more serious operations and should not be performed unless all the *pros* and *cons* have been seriously considered.

Is there a condition of splenic thrombocytopenia? Certainly in the presence of splenomegaly a well-defined thrombocytopenia is present in most cases. Whether the thrombocytopenia of idiopathic thrombocytopenic purpura (ITP) is hypersplenic is now a matter of dispute, although some years ago this seemed reasonably clear. The association of thrombocytopenia in the blood with well-defined increases in megakaryocytes in the marrow, the latter cells showing but little platelet production, and the striking platelet production following splenectomy, all seemed to indicate quite clearly that the spleen was concerned in the thrombocytopenia. Recently, however, the immunologic nature of ITP has come to the fore,[28] and it is possible that most of the features of the disease are due to the immunologic abnormality and not to a more or less hypothetical splenic humoral effect. It is difficult, however, on this basis, to explain the striking thrombocyte production that occurs so quickly after splenectomy, possibly indicating the removal of an inhibitory factor. It is also likely that ITP may be a disease of variable pathogenesis, and that some cases may be immunologic and others hypersplenic.

Not Hypersplenism

At this time, what is *not* hypersplenism should be discussed, especially since certain conditions resembling hypersplenism superficially, or which have been called hypersplenism by various observers may actually be examples of a more fundamental disturbance in which the spleen becomes enlarged secondarily. This is well exemplified in the cases of *hereditary spherocytosis*. Here, there is an hereditary defect of red cell production with the presence in the blood of variable numbers of small, unusually thick red blood cells called spherocytes. These cells, apparently because of their unusual shape, are trapped by the normal spleen,

sequestered there, and ultimately destroyed.[29] The life span of the spherocyte is, therefore, very short. Because the spleen is called upon to sequester and destroy more cells than is normal, it gradually becomes larger. This is not hypersplenism in the sense of our definition but is simple splenomegaly occurring in response to an outside factor, in this instance, the presence of spherocytosis. That hypersplenism is not a factor is indicated by the short survival time of the hereditary spherocytes when they are transfused into an individual having a normal spleen. Again, the transfused spherocytes are selectively trapped, and are removed quickly, even though by a normal spleen. Conversely, when the spleen is removed from a patient with hereditary spherocytosis, the red cell life span becomes normal, and the anemia previously present becomes completely corrected. Thus, in this disease, the fundamental disturbance is a defective red blood cell; there is no evidence, except possibly in a crisis, of an inhibitory mechanism,[30] and the phagocytosis is a normal splenic response to spherocytosis. In *auto-immune acquired hemolytic anemia*, the situation is quite different. Here, the red cells are produced in normal fashion by the bone marrow. They appear in the circulation as entirely normal cells, but are then attacked by antibodies which have the capacity of fixing themselves on the patient's own red blood cells, i.e., they are auto-antibodies. These abnormal protein materials are apparently produced by such antibody-producing tissues as the systems of the lymphoid, plasma cell, and the reticuloendothelial cells. As the result of the antibody attack, the red blood cells become injured and thus spherocytic to greater or less degree; they are then trapped by the spleen, as in the case of the hereditary spherocyte, phagocyted, and ultimately removed. Thus, their life span is distinctly shortened. This is not hypersplenism in the sense that we consider it, but simply splenomegaly on the basis of extra work by that organ, both by reason of phagocytosis and perhaps also on the basis of excessive antibody production. Here the fundamentally abnormal condition is the antibody productive mechanism and not a primary disturbance in the spleen.

Acute idiopathic thrombocytopenic purpura is also not hypersplenism. Here, the patient probably develops an abnormal immuno-allergic mechanism following either an acute infection or the intermittent use of a chemical. There is a rather sudden hemorrhagic disturbance characterized by petechiae, ecchymoses and bleeding from the mucous membranes. Because of apparent injury to the megakaryocytes in the bone

marrow, and the rapid destruction of the platelets in the circulating blood, the platelet level becomes very low. The spleen appears to have little, if any, relationship to the development of this disorder and most cases develop a normal blood platelet count spontaneously. We have concluded[31] that splenectomy is ordinarily not indicated in these cases, both because the operation in acute thrombocytopenia may be quite dangerous, and the patient makes a spontaneous recovery in at least seven cases out of ten. In the meantime, the patient is treated with blood transfusions given from plastic bags, in which the platelets are preserved, and by large doses of ACTH.[28b] With this procedure, the great majority of patients recover completely after several anxious weeks. Here, the fundamental disturbance is not in the spleen but rather in an immunologic mechanism. In chronic ITP the question of hypersplenism still remains, at least in those cases in which an immunologic mechanism cannot be demonstrated. Even when it can, however, the striking effects of splenectomy, as witnessed in the explosive production of platelets by the megakaryocytes, speak in favor of the possibility of a hypersplenic component.

Splenectomy

This brings us to a consideration of splenectomy, its indications, and its contraindications. When should splenectomy be performed? I have made three categories for this: "Yes," "No," and "Maybe." In the "Yes" category, the undoubted indication for splenectomy is splenic rupture, either following trauma, or in the course of an acute infection, such as infectious mononucleosis or malaria. Here, once the diagnosis is made, the patient should be operated upon as expeditiously as possible, else death may ensue. The other absolute indication for splenectomy is that of hereditary spherocytosis. Even in the presence of a relatively mild condition, splenectomy should be performed for two reasons: 1) Bilirubin production is greatly increased, even in the mildest cases, and as a result large amounts of bile pigment are constantly passing through the liver, bile ducts and gallbladder. Gallstone formation occurs in at least 75 per cent of the cases and sooner or later may cause trouble. 2) Each case of hereditary spherocytosis, however mild, is subject at some time during the patient's course to the development of crisis. This may occur early in life or not until the age of fifty or sixty. In the crisis, the red blood count may go from 4 million to 1 million in a period of twenty-

four hours. Occurring in a young child, this is serious enough, but in an adult it causes a considerable strain on the heart muscle and may even result in death. The fundamental cause of the crisis, whether it is related to hypersplenism or to "aplasia" of the red cell element, remains at present obscure.

Chronic ITP is a well-defined indication for splenectomy because no other good therapeutic method is presently at hand for the treatment of these cases. Splenectomy is curative in at least 60 per cent of the cases; in 20 per cent the remissions are slight, but in about 20 per cent, there is complete failure. In splenic neutropenia, splenic pancytopenia, hypersplenic hemolytic anemia, and hypersplenic thrombocytopenia, the indications for splenectomy are well-defined, and the results of operation are about 80 per cent curative. In those cases in which the results of the operation are either nil or very slight, the conclusion must be reached that the initial diagnosis of hypersplenism was in error. It is well to remember, however, that a certain statement as to the eventual result of splenectomy in a given case cannot be made for at least six months, as I have noted complete and sustained remissions that have developed at the end of that time.

As for the "No" group or the contraindications to splenectomy, in what at first glance appears to be hypersplenism (splenomegaly, cytopenias, hyperplastic bone marrow) leukemia is ordinarily a reason for not removing the spleen. This rule has its exceptions, however, and we have seen brilliant results following operation in occasional cases, particularly in those requiring numerous transfusions. In infections that can be reversed by appropriate therapy (malaria, subacute bacterial endocarditis) splenectomy should not be performed except for impelling reasons. It should also not be done in the acute self-limited type of idiopathic thrombocytopenic purpura, which we conceive of as a self-limited disease in the great majority of the cases, the fundamental mechanism being an immuno-allergic one. Splenectomy here entails a considerable risk for the patient; most cases have a completely beneficial result spontaneously.

Is emergency splenectomy ever indicated?[32] We believe it is, but only in the case of rupture. In the hemolytic crisis of hereditary spherocytosis, it is best to place the patient in as good condition as possible by the use of transfusions and fluids to restore the water and electrolyte balance. Splenectomy can then be performed at leisure, in the presence of a

"quiet" patient. In acute idiopathic thrombocytopenic purpura, as already stated, splenectomy is best left alone. In the hemorrhagic crisis of the chronic form of the disease, the patient is best treated with ACTH and plastic bag transfusions. When the usual state of mild purpura and thrombocytopenia have then ensued, splenectomy can be performed as an elective procedure. This precaution has been very beneficial in improving the mortality rate of the operation.

In the "Maybe" group of cases, one must now list myeloid metaplasia of the spleen in association with myelofibrosis of the marrow, although at one time this condition was considered an absolute contraindication to splenectomy. This concept was based on the idea that the marrow had become almost completely fibrotic and that the spleen contained almost all the blood-producing tissue in the body. However, from a number of sources, it has become evident that splenectomy in this disease need not necessarily be fatal,[33] and that a well-defined remission may occur with operation, perhaps through the removal of the inhibitory factor of the enlarged spleen, perhaps through some other means. The operation should be considered only if the transfusion requirement is becoming more and more marked, or the platelet level relatively low. Under these circumstances, splenectomy may be followed by striking remissions. A complication of great significance is the tendency to thrombosis, often quite striking because of the marked increase in platelet level. This must be realized before operation is attempted.

There can be no doubt from this and other considerations that in certain cases a gamble or a calculated risk in carrying out splenectomy may ultimately result in a striking benefit for the patient. Thus, in certain cases of hypoplastic anemia, particularly when the marrow is relatively cellular, and in cases of so-called "refractory" or "adynamic" anemia with pancytopenia in the blood and a cellular marrow, splenectomy may be of distinct value, even in the absence of splenomegaly. The results may not be obtainable immediately, but there may be a gradual improvement and ultimately normal or near normal hematologic values may be reached. In other cases in which the marrow seems totally fibrotic and the transfusion requirement is particularly great, too great for hypoplasia alone, splenectomy may be followed by a brilliant result. We have seen this not only in myelofibrosis of the idiopathic type, but in the fibrosis of certain cases of lymphocytic leukemia. Certain cases of pure red cell hypoplasia are also benefited by splenectomy, but which ones will be

benefited and which will not, can unfortunately, not be predicted in advance of operation.[34] In such cases, the administration of cortisone may be temporarily effective, and if this occurs, as Loeb and Moore have indicated, splenectomy may be permanently so. Selected cases of Mediterranean anemia, particularly those in which anemia of moderate degree of severity is present in association with well-defined splenomegaly, icterus, and the indications of increased hemolysis, may be moderately well-controlled by removing the spleen. In this disease it is well to realize that the fundamental disorder is unmodified but the need for transfusions may be considerably diminished. In some cases of auto-immune hemolytic anemia not responding well to ACTH and cortisone, splenectomy should be considered and may eventually be followed by a complete remission. In certain cases of leukemia, removal of the spleen may be of distinct benefit;[35] for example, some cases of lymphosarcoma and leukemia are associated with continued pancytopenia and with the need for numerous transfusions. In these cases, the survival time of introduced red cells may be distinctly shortened, even though no gross evidences of increased hemolysis are present (occult hemolytic anemia). Careful studies in such cases will reveal 1) a shortened red cell survival time of introduced blood; 2) a slight though definite reticulocytosis of 2 to 5 per cent; and 3) an increased amount of urobilinogen in the feces. The transfusion requirement in these cases may be distinctly benefited to a greater or less degree by splenectomy. How much benefit will accrue in an individual case cannot be stated, but if the gamble is taken, some cases may show a striking and even remarkable effect. In one such case requiring transfusion at weekly intervals, removal of the spleen was followed by a rise in the red cell and hemoglobin values to normal and in a complete cessation of the need for transfusions.

Finally, the statement should be made that splenectomy may be undertaken in various peculiar hematologic cases characterized by varying cytopenias in the absence of splenomegaly. It is well to remember, however, before the final decision on splenectomy is made, that all fundamental diseases such as leukemia, the collagen disorders, certain infections like malaria, etc. should be ruled out as far as possible; otherwise, the end-result might be embarrassing. Each case should be carefully evaluated and judged on its merits and a thorough going-over of the pros and cons should be made.

Summary

In this lecture we have discussed at some length our concept of hypersplenism, which is based chiefly on the possibility that a large and presumably abnormal spleen exerts an undue effect on the marrow blood cells. It is possible that hypersplenism represents simply an accentuation of the normal regulatory effect of the spleen (splenism) on the bone marrow. Thus, the spleen tends to have an inhibitory effect on the red cells, granulocytes and on megakaryocytes-platelets. In the presence of splenomegaly of many types these inhibitory effects are exaggerated with the result that various cytopenias occur. Under such circumstances the marrow is hypercellular but the blood is cytopenic. In the presence of marked degrees of cytopenia as with neutropenia, thrombocytopenia, anemia, or combinations of these three, the individual's life may be placed in jeopardy. Under such circumstances splenectomy must be seriously considered as a therapeutic procedure and in many cases is followed by highly beneficial result. Hypersplenism, although unproved as a definite entity, is nevertheless an important clinical concept from the diagnostic and therapeutic standpoints. Until medical measures are advanced for dealing with it, the necessarily crude operation of splenectomy will have to be continued as a prime method of therapy.

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A NEW AND SIMPLE TEST FOR HYPERTHYROIDISM EMPLOYING L-TRIIODOTHYRONINE AND THE TWENTY-FOUR-HOUR I-131 UPTAKE METHOD*

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THE administration of thyroid, thyroxine or triiodothyronine causes a sharp reduction in I-131 uptake by the thyroid in euthyroid subjects[1-4] but little if any change in Graves' disease.[4-6] This distinction is so clear-cut that an investigation was undertaken to establish whether the reaction would be as useful diagnostically as these results implied. Since thyroid contains iodides and several organic iodinated compounds which might induce false positive results, and since also the effects of thyroid and of thyroxine are protracted after treatment is discontinued, crystalline-triiodothyronine was chosen as the test agent. The material is available in pure form and has a more rapid half-life within the body than thyroxine.[7] While this study was being pursued, Greer[8] independently was investigating the use of thyroid for the same purpose and obtained similar results.

METHODS

Patients with a variety of clinical disorders were tested. Pills containing 35 μg. of triiodothyronine were employed at first but the strength was reduced during the experiment to 25 μg.† Thus doses varied during the experiment from 70 to 75 and 140 to 150 μg. given daily for eight days by mouth. Dosage was begun after an initial twenty-four hour I-131 thyroidal uptake was determined, using a 15 μc. dose of I-131; measurements were made directly over the thyroid by means of a bismuth cathode Geiger tube. On the eighth day of triiodothyronine treat-

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TABLE I—TABLE SHOWING DISTRIBUTION OF INITIAL TWENTY-FOUR HOUR I-131 UPTAKE VALUES

Patient Category	*No. Patients*	*Initial 24 hour I-131 uptake %*		
		39 or less	40-54	*55 or more*
Euthyroid controls	48	30	13	5
Nontoxic goiter				
diffuse	16	8	7	1
nodular	19	14	4	1
Untreated toxic goiter	48	2	13	33
Treated toxic goiter, euthyroid	12	9	2	1
Early eye signs of Graves' disease, euthyroid	10	6	3	1
Total	153	69	42	42

ment, residual radioactivity in the thyroid was measured and 15 μc. I-131 administered for the second time. The next day, uptake was determined, allowance being made for the I-131 remaining from the initial test. The lapse of eight days following the start of treatment was suggested by early studies with small and large doses of triiodothyronine given daily with uptake measured at varying intervals from the start of treatment. Six patients were given a single 500 μg. dose of triiodothyronine and the uptake followed daily. Uptake began to decrease after as little as forty-eight hours but did not reach a minimum uniformly, requiring between three and eight days for the complete response to be achieved.

All patients were examined by one of us (S.C.W.) and the diagnosis established on clinical and laboratory grounds other than the response to triiodothyronine subsequently obtained.

RESULTS

A total of 138 patients were given triiodothyronine diagnostically. The various patient categories are listed in the tables. All patients used as control subjects and without demonstrable thyroid disease are grouped together under the heading "euthyroid controls." This group is heavily weighted with high initial uptake values because of the effort to collect

TABLE II—SUMMARY TABLE SHOWING THE EFFECT OF TRIIODOTHYRONINE UPON TWENTY-FOUR HOUR I-131 UPTAKE. THE SMALLER NUMBER AFTER THE MEAN GIVES THE STANDARD ERROR OF THE MEAN.

Patient Category	*No. Patients*	*Daily Dose Triiodothyronine μg.*	*Average 24 Hour I-131 Uptake Before*	*After*
Euthyroid controls	41	75	37 — 2.2	12[1]— 1.4
	7	35	30	10
Nontoxic goiter				
diffuse	16	75	40	9[2]
nodular	13	75	34	15[3]
	8	150	31	14
Untreated toxic goiter	20	75	56 — 3.4	62[4]— 3.4
	28	150	63 — 9.0	63[4]—11.1
Treated toxic goiter, euthyroid	12	75	34	15[5]
Early eye signs of Graves' disease, euthyroid	10	75	34	32[6]

Footnotes—1. One value 36%, falling to 1% with 150 μg. daily.
2. One value 26%.
3. Three values more than 20% (24%, 27%, 30%).
4. No value less than 35%.
5. Two patients showed no response and were subsequently found to have active disease.
6. Two patients included received thyroid daily 0/12 Gm. and 0/18 Gm. respectively for 8 days.

TABLE III—TABLE SHOWING PER CENT DECREASE IN I-131 UPTAKE (INITIAL UPTAKE-FINAL UPTAKE) RESULTING FROM TRIIODOTHYRONINE ADMINISTRATION

Patient Category	*Change in uptake (%)*				
	±0 or increase	—1 —9	—10 —19	—20 —29	*—30 or less*
Euthyroid	1	2	8	16	14
Nontoxic goiter					
diffuse	0	0	3	5	8
nodular	1	6	7	2	5
Untreated toxic goiter	33	11	3	0	1
Treated toxic goiter	0	3	2	6	1

such patients for study. The nontoxic goiter group has been divided into diffuse and nodular but this has not been done for the toxic goiter group because no difference between the responses of toxic diffuse and toxic nodular goiter was evident.

Eighteen of forty-eight euthyroid control patients (37 per cent) had initial uptakes of 40 per cent or more; fifteen of forty-eight hyperthyroid patients (31 per cent) had initial uptakes less than 54 per cent (Table I). The percentages of overlap are somewhat less for the nontoxic nodular goiter group and somewhat more for the nontoxic diffuse group but the number of patients is small.

In all groups except toxic goiter and the euthyroid patients with the early signs of Graves' diseases, the administration of 75 μg. triiodothyronine daily for eight days resulted in a uniform decrease in I-131 uptake to 20 per cent or less (Tables II and III). There was one exception in the euthyroid control group in which the uptake increased from 24 per cent to 36 per cent with 75 μg. triiodothyronine daily, but with a dosage of 150 μg. for eight days, the uptake was depressed to 1 per cent. A daily dose of 35 μg. was given to seven euthyroid control patients with all but one patient having an uptake less than 20 per cent on the eighth day of treatment. In the nontoxic diffuse goiter group, one of the sixteen patients had an uptake which failed to decrease to less than 20 per cent, although a decrease had occurred from 44 per cent to 26 per cent; uptake was not further reduced by daily doses of 150 μg. triiodothyronine. Five of the twenty-one patients in the group with nontoxic nodular goiter, three with single nodules in the gland and two with multiple nodules had uptakes after triiodothyronine administration between 20 per cent and 30 per cent, the rest being less than 20 per cent. Their initial twenty-four hour I-131 uptakes within the normal range did not suggest hyperthyroidism. Radioautographs of the specimens obtained at operation upon three of these patients revealed significant uptake by the nodules as well as by the parenchyma of the gland.

In the toxic goiter group, no I-131 uptake was less than 35 per cent following triiodothyronine doses of either 75 or 150 μg. A group of ten euthyroid patients with early eye signs of Graves' disease was observed (Fig. 1) in whom uptake failed to respond to the administration of triiodothyronine, even though the initial uptakes were within the normal range, exceeding 45 per cent in only two instances. This was

Fig. 1A

Fig. 1B

Fig. 2

Fig. 1—A. and B. Euthyroid patients D.S. and M.E. with early eye signs of Graves' disease. The I-131 uptake did not decrease upon triiodothyronine administration.

Fig. 2—Patient E.R. with acute myeloblastic leukemia involving the orbits. I-131 uptake fell in response to triiodothyronine dosage.

in contrast to twelve patients with residual eye signs of Graves' disease after remission from the hyperthyroidism had been induced previously by definitive therapy. A sharp drop in I-131 uptake was noted in all but two of the latter upon triiodothyronine administration, and these two patients shortly thereafter became more obviously ill of recurrent disease. In three additional patients with eye signs which created confusion diagnostically with those of Graves' disease but subsequently proven to have other diseases, a normal response to triiodothyronine was observed and uptake dropped to less than 20 per cent. Two of these had pseudotumor of the orbit and one, acute myeloblastic leukemia (Fig. 2).

The extent of decrease in I-131 uptake following triiodothyronine dosage is of interest (Table III). Forty-four of the forty-eight toxic goiter patients responded with a decrease of less than 10 per cent whereas thirty-eight of the forty-one euthyroid control subjects had decreases in excess of 10 per cent and in fact thirty of the forty-one a decrease exceeding 20 per cent.

Discussion and Conclusions

The present study indicates that the response of the twenty-four hour I-131 uptake by the thyroid to the administration of triiodothyronine in 75 to 150 μg. doses offers a clean-cut separation between toxic goiter and euthyroid subjects without thyroid disease. Euthyroid subjects with one exception had an uptake of 20 per cent or less following treatment with 75 μg. daily whereas in no instance was the final uptake less than 35 per cent in toxic goiter even when 150 μg. daily were given. The one exception among the euthyroid patients responded with a 1 per cent uptake when 150 μg. were given.

Patients with active hyperthyroidism can also be differentiated with this technique from patients with inactive disease in whom a sustained remission had been induced by definitive therapy; and also from patients with nontoxic diffuse and nontoxic nodular goiter. The test is simple and requires only the performance of two I-131 uptake tests, one before, and a second after triiodothyronine has been taken by mouth for a week. No special equipment is required beyond that needed for the twenty-four hour I-131 uptake method alone and the test is useful for the ambulatory patient.

A dose of at least 75 μg. daily is suggested to insure uniformity of response by the euthyroid patients. Although Starr[8] observed a decrease in uptake with as little as 8 μg. daily in healthy subjects, 35 μg. given daily in the present series resulted in one failure in seven patients tested, and one patient was seen who did not react to 75 μg. although responding vigorously to twice that amount. No side reactions have been observed from the use of triiodothyronine at the 75 μg. dose level which could not have been attributed equally to anxiety. At the 150 μg. level, euthyroid patients generally complain of mild increase in tension and nervousness; infrequently, epigastric fullness, increased palpitation, nausea and vomiting, paroxysmal hacking cough, or headache may occur. One patient only could not complete the test because of nausea,

vomiting and palpitation on the larger dose but her physician stated this occurred with all medication. No definite evidence of increase in the toxicity of existing hyperthyroidism has been observed. Symptoms generally subside within a day or two of stopping the drug.

About a third of values for the initial twenty-four hour uptake in the euthyroid patients of the present series exceeded 40 per cent, some extending beyond 50 per cent (Table I). Values in this range were not conclusive diagnostically because about a third of initial values in untreated hyperthyroidism were less than 55 per cent extending rarely below 40 per cent (Table I). In a larger series from the routine laboratory of the hospital in which the factor of selection weighted the percentages less, this figure was somewhat less, 16.4 per cent of patients having indeterminate uptakes. It is in clarifying the diagnosis of this group of patients that the use of triiodothyronine serves its largest purpose.

Patients with eye signs suggestive of Graves' disease should be tested with triiodothyronine regardless of the initial uptake value. The identification of a group of euthyroid patients with recent onset of typical early eye signs of Graves' disease was made possible by their failure to respond to triiodothyronine. The failure of the uptake to be suppressed by triiodothyronine administration to this group suggests that these patients have active Graves' disease despite their euthyroidism: the response conforms to that of patients with active Graves' disease.

The response to triiodothyronine in active Graves' disease is in sharp contrast to that of patients brought into remission from the disease by successful treatment and tested after having been well for one to fifteen years. In these latter patients, a normal response to triiodothyronine was noted in all but two, and these two shortly developed overt hyperthyroidism. It would thus appear that the test may be useful in establishing activity of the eye complications of the disease, as well as of the hyperthyroidism. One euthyroid patient was tested twice, during the period of active ophthalmopathy after subtotal thyroidectomy, and after the onset of spontaneous remission. Uptake was unchanged by triiodothyronine treatment in the active phase, 22 per cent initially and 20 per cent after; but was decreased definitely in the phase of remission, 19 per cent initially and 9 per cent after. By the same token, patients with eye signs simulating those of hyperthyroidism but due to other diseases, can be distinguished from Graves' disease. Three such patients

were tested and showed a normal decrease in I-131 uptake following triiodothyronine administration.

About half of the initial twenty-four hour I-131 uptake values in patients with nontoxic diffuse goiter in the present series were 40 per cent or more. The responses when triiodothyronine was given were like those of the control subjects without thyroid disease. One patient did not respond well but the final value was 26 per cent which was less than the lowest value of 35 per cent occurring in toxic goiter in response to the agent.

The patients with nontoxic nodular goiter in whom uptake failed to decrease upon triiodothyronine administration have not constituted a difficult diagnostic problem since initial and final uptakes were within the normal range. Radioautographs of surgical specimens of the thyroids of three of these five patients were made at a later date and revealed the nodules to have been about as functional as the surrounding normal tissue. This finding is being pursued in order to determine if the thyroid parenchyma, the nodules, or neither, become inactive functionally in response to triiodothyronine.

Summary

1. Triiodothyronine, 75 or 150 micrograms daily by mouth for eight days, caused a sharp decrease in the twenty-four hour I-131 uptake in forty-eight euthyroid patients without thyroid disease so that no value exceeded 20 per cent. In contrast, no value under 35 per cent was obtained in patients with toxic goiter following triiodothyronine administration. Side effects occurred in euthyroid patients only, with a dosage of 150 μg. and were relatively minor.

2. About a third of the euthyroid patients in this series had initial twenty-four hour I-131 uptake values in excess of 40 per cent, and a third of the hyperthyroid patients had uptakes less than 55 per cent. Triiodothyronine was virtually specific in clarifying the diagnosis in this group with overlapping values.

3. Triiodothyronine was valuable in establishing the activity of the eye complications of Graves' disease. Euthyroid patients with the early eye signs of Graves' disease and patients with overt hyperthyroidism showed an abnormal response to triiodothyronine but patients in sustained remission reacted normally.

4. Patients with nontoxic diffuse goiter responded like normal

subjects to the administration of triiodothyronine, whereas five of the twenty-one patients studied with nontoxic nodular goiter had no response to triiodothyronine administration, even though the initial uptake values were within the normal range. Radioautographs of three of these glands revealed the nodules to be functionally active.

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NEW YORK PATHOLOGICAL SOCIETY AND NEW YORK ROENTGEN SOCIETY

*Abstracts of Papers and Discussion**

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Correlation of Radiographic and Autopsy Findings in Suspected Metastases in the Spine

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Routine correlation studies of ante-mortem x-ray appearance and autopsy findings suggested that in an unexpectedly high percentage of cases there were metastases in the spine which were not visible on the radiographs. This impression was tested by a more detailed investigation concerning 1) the incidence of spinal metastases which could not be radiographically demonstrated and 2) some of the factors affecting the demonstrability of spinal metastatic deposits by roentgen ray.

Fifty-nine cases were selected at random and the results of the following studies in each case recorded:

(a) Last ante-mortem x-ray of the spine.

(b) Postmortem Bucky of the spine in the anteroposterior position.

(c) Postmortem anteroposterior tomography of the spine.

(d) Radiograph of spinal segments removed at autopsy.

(e) Histopathology of sections of the spine.

Pathologically, thirty-one of the fifty-nine cases were found to show spine metastases. In these thirty-one cases the metastases could be subdivided into osteoblastic—nineteen cases; osteolytic—five cases; mixed osteoblastic osteolytic—two cases; intertrabecular—five cases. The intertrabecular metastases were those in which the deposits were limited to the marrow spaces between the trabeculae and the latter were not affected. As a result, there was no change in any of the bony elements of the spongiosa or compacta portions of the vertebrae. The osteoblastic lesions were characterized by local or diffuse thickening and fusion of trabeculae. Increased bony deposition was noted in response to the presence of malignant cells in the adjacent marrow spaces. On the other hand, the osteolytic lesions showed focal or generalized thinning and destruction of trabeculae in the spongiosa, or similar osteolysis of the denser cortex. Areas of asymmetric collapse and compression, due to the irregular destruction, were seen in the involved vertebral bodies. Mixed lesions demonstrated non-patterned alternating areas of osteolysis and blastic changes.

Of the thirty-one cases with pathologically proved metastases, in only fifteen (48.4 per cent) were the metastases visualized by the x-ray examinations, including the anteroposterior routine Bucky and tomographic studies. The value of the radiographic examination in detecting the various types of

* Manuscripts received July 1954.

metastatic deposits may be seen from the following table:

Type of Metastasis	*Number of Cases*	*Visualized by X-Ray*
Osteoblastic	19	8
Osteolytic	5	4
Mixed lytic and blastic	2	2
Intertrabecular	5	1
Total	31	15

The intertrabecular lesions were least successfully demonstrated, in only one of the five cases. This finding was expected, as these deposits were found not to affect significantly the bony structure of the vertebral bodies, and the radiographic examination of the spine reveals only the bony changes. Indeed, in the case where it was recognized, the x-ray changes, osteoblastic in type, were minimal. It is also quite probable that even in this case there were beginning osteoblastic changes superimposed upon the intertrabecular deposit.

The osteoblastic deposits could be recognized radiographically in only eight of the nineteen cases (42 per cent). Even lesions considerably greater than 1.5 cm. in diameter were not demonstrable in several instances. In only a few of these cases was the form or contour of the involved vertebral body altered. The osteolytic and mixed lesions were demonstrated much more frequently. Recognition of these lesions was aided in part by changes in form and contour of the vertebrae. The osteolytic metastases were frequently accompanied by collapse of vertebral bodies.

In twenty-eight cases there were no metastases to the spine at autopsy. A "false positive" diagnosis of metastases was made in only one instance, a case with marked hypertrophic eburnation of the articular plate and subarticular spongiosa of the vertebral body. Indeed, even at autopsy the findings suggested osteoblastic metastases, and only microscopic study revealed the condition to be non-neoplastic, simple degenerative sclerosis.

The demonstrability of spinal metastases was assessed against the site of the primary tumor and the histologic type of the neoplasm. Neither of these factors showed a significant association with, or played an apparent role in the radiographic visibility of the metastases.

The size of the metastases was found to be of critical significance in their radiographic recognition. As a preliminary study, vertebral bodies were resected at autopsy and holes of various diameters and depths were drilled into them. These holes were filled with paraffin (to simulate tumor tissue) and the vertebrae were x-rayed in air. The paraffin was then removed and the vertebrae were placed in a large body-simulating water phantom and again radiographed. Routine anteroposterior and lateral views were obtained, followed by anteroposterior and lateral tomographic studies. The resulting radiographs showed that the holes were better visualized in the lateral views than on the anteroposterior views. A hole 0.6 cm. in diameter was well demonstrated on the film taken of the vertebra in air, but not definitely shown when the vertebra was in the water phantom. The scattering effect on the x-rays by the "body" was observed to be a significant factor in obscuring details of trabecular pattern and in causing small holes to be imperceptible on the radiographs. It appeared that in vivo, destructive lesions one cm. in diameter or less in the vertebral body probably would not be visualized on the radiographs. Lesions between 1.0 and 1.5 cm. in diameter might be visualized, and larger volumes of destruction probably would be demonstrable. The tomographic studies of the isolated vertebral bodies resulted in somewhat better visualization of several, but not all, of the drilled holes. In some instances, holes of small size could be seen on the tomographs, whereas they were not observed on the comparable conventional radiographs. However, in other cases body-section roentgenography did not permit more satisfactory visualization of the defects.

Further investigation of the value of tomography was pursued with a "clinical" trial. Anteroposterior conventional and tomographic studies were made post mortem, immediately prior to autopsy. These resulted in very satisfactory roentgenograms identical with those obtained during ante-mortem clinical radiography. It was found that the metastases were not visualized by the conventional x-ray study in fifteen of the thirty-one positive cases, and were imperceptible

on the tomograms also in fifteen cases. These cases were not identical. In two cases the tomograms revealed lesions not seen on the conventional films, while in several cases the conventional radiographs demonstrated metastases that could not be recognized tomographically. In the remaining cases, both the conventional and body-section x-ray studies failed to reveal the pathologically proved metastases that were present. It thus appears that body-section roentgenography is not sufficiently superior to conventional radiography of the spine in revealing metastatic deposits to warrant its routine use for the exclusion of asymptomatic lesions. Its place appears reserved for those cases with symptoms where the routine x-ray studies are unrevealing. By its use occasional success in demonstrating otherwise occult metastases may be expected.

In conclusion, the study showed that in sixteen of thirty-one cases with pathologically proved metastases the deposits could not be demonstrated radiographically. Many of these metastases were of rather large size. Anteroposterior tomography was not more successful than the conventional radiographs in revealing the occult metastases.

Factors in Bone Equilibrium

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In order to dovetail better with the succeeding paper this evening, I will chiefly discuss factors in bone equilibrium concerned with the development of osteoporosis with a small digression on some interesting but mysterious bone abnormalities. Osteoporosis has been defined as demineralized bone due to inadequate matrix. While this definition is useful in separating this condition from osteomalacia, it implies a mechanism that has not yet been proven correct, and has not even been demonstrated experimentally. Perhaps in our present state of knowledge it is better to recognize osteoporosis only as very thin bones, and scrutinize some of the mechanisms associated with it. Some of the common conditions associated with osteoporosis are immobilization, malnutrition, scurvy, Cushing's syndrome (either natural or iatrogenic), the postmenopausal state, and old age. Unfortunately, not so rarely, the osteoporosis is utterly idiopathic. One of the most intriguing and totally unexplained aspects of osteoporosis is what makes it symptomatic. Even using something as crude as the x-ray, demineralized bones are very commonly found, especially in older people. In the vast majority of instances there are no symptoms, but in a few with no more apparent thinning there will be severe pain and discomfort. The lack of correlation with the available signs is so far unexplained.

It is well known that immobilizing an extremity with plaster of Paris, or the whole body as in quadriplegia, leads to a negative calcium balance, and demineralized bones. This change has been ascribed to a lack of stress, and hence no stimulus to osteoblastic activity. It is presumed that resorption goes on at a normal rate. And indeed, if these patients are placed on an oscillating bed, which certainly induces a kind of stress, they do not have a negative calcium balance. This would point very conclusively to stress as being the main factor. But is it the only factor?

When there is immobilization, there is also a diminished blood supply to the part, and when one is on an oscillating bed there is an increased blood supply. It is hard to answer what part the diminished blood supply may play in demineralization. But we can digress a minute and see what too much blood does to the bone of someone still capable of growth. On the roentgenogram

shown are three hands: There is a normal control, and then the right and left hands of a patient with acromegaly. The left hand is much larger than the control, with somewhat thicker bones. This is certainly the effect of growth hormone. But the patient's right hand is even larger, and in the photograph there are many prominent veins, and indeed the hand is a great deal warmer than the left. This patient has multiple congenital arteriovenous aneurysms in the right arm, and the increased blood supply to this hand before the epiphyses could close has induced this tremendous overgrowth. The basic mechanism by which this overgrowth is produced is obscure. Although increased blood flow may cause overgrowth, the effects of decreased blood flow are less certain, and in all probability the main factor in the osteoporosis of disuse is the lack of stress rather than changes in the circulation.

There is another interesting condition that results in an overgrowth of normal bone. These roentgenograms and photographs show a case of neurofibromatosis with minimal soft tissue changes and a gigantic increase in the length of one leg. In the films of this leg the bony structure appears essentially normal, but biopsies on two occasions have shown a plexiform neurofibroma. The long leg is about 4° warmer as measured with a thermocouple, so that it is possible that an increase in circulation is a factor. The underlying mechanism for this kind of overgrowth is also obscure, however.

But to return to osteoporosis, the situation as regards malnutrition would seem straightforward. With lack of protein, there might well be an inadequate formation of matrix, and if there were a shortage of minerals as well, there would be a mixed picture. And in scurvy, there is certainly a shortage of ground substance.

It is with cortisone that our main interest lies. Serial roentgenograms are shown of a man who has pemphigus, but was not immobilized, and it can be seen that several vertebrae have abruptly collapsed, with really very little change in the density of the bones as measured by the serial x-rays.

It is very tempting to go along with the theories of Fuller Albright[1] that the cortisone by an anti-anabolic effect is blocking the synthesis of matrix. Blunt and his coworkers[2] certainly noted a diminished production of a mucopolysaccharide in experimental fractures of animals treated with ACTH. It is also true that Layton[3] noted a failure of synthesis of chondroitin sulfate when cortisone was added. And for a relatively long time the mutually antagonistic effects of cortisone and growth hormone have been known. But, on the other hand, it is very difficult to demonstrate any inhibitory effect of cortisone on bone matrix.

Follis[4] has shown that the changes in the epiphyseal cartilage of cortisone-treated rats were essentially no different from the changes in those rats which lost an equivalent amount of weight due to starvation. Both showed a narrowing of the epiphyseal cartilage due to a reduction in the number of hypertrophic cells, and a retardation in the proliferation of undifferentiated cells. But the most striking difference in the cortisone-treated rats was an increase in the amount of calcified cartilaginous matrix encased in bone in the spongiosa. This finding would suggest a stimulation rather than a depression of the matrix.

Wolbach[5] showed in scurvy, where there is indeed a deficient matrix, that the administration of cortisone did not modify the development of scurvy, nor affect its cure with vitamin C. New matrix was laid down regardless of the presence or absence of cortisone. Also in some studies on low phosphorus rickets, where there is an exceedingly abundant matrix, Payson and I were able to show that there was no inhibiting effect of cortisone on the appearance of the rickets. The rickets was slightly less severe in the cortisone-treated rats, but this might have been because they lost more weight than the controls, or because of an increased calcification similar to that shown by Follis. At all events they were well able to make matrix. Perhaps, therefore, we should have a few reservations about attributing the demineralization of bones seen after administration of cortisone to a blockage of matrix.

The remaining conditions, the postmenopausal state and old age, are very commonly associated with osteoporosis and, as previously indicated, under the circum-

stances it is remarkable that the disorder is not more frequently symptomatic, or that it is ever symptomatic.

I want to reiterate that at the moment osteoporosis should be recognized as a stage of demineralized bones in the presence of normal serum minerals, without implying a failure of matrix. While the matrix may not be adequate there is as yet no direct evidence on this point.

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DISCUSSION

ALEXANDER B. GUTMAN: Dr. Plimpton has indicated to you that the problem of osteoporosis involves more than protein balance. As he pointed out, the laying down or removal of bone is dependent on such well defined, although not well understood, factors as vascularization of the bone, activity or stress, and the action of endocrines.

It would seem hardly necessary to emphasize the point that osteoporosis involves loss of bone mineral as well as loss of bone protein. Historically, the earlier view was that osteoporosis was the result of extensive decalcification or demineralization of bone, the emphasis being on the loss of bone mineral, with very little or no attention being paid to the matrix. Macerated specimens of bone in senile osteoporosis, for example, give striking visual evidence of the loss of mineral from the bone substance. About ten or fifteen years ago, there came a sharp reaction to this one-sided view, stressing the importance of the protein matrix. Albright was one of the leaders in this field. Bone does contain a very substantial amount of matrix protein. It was inferred that loss of this protein must occur in certain circumstances, such as after the menopause, particularly when there is a diminished protein intake, but proof of that was never brought forward, to my knowledge. Administration of estrogens and androgens, which effect some nitrogen storage, also ameliorate pain in postmenopausal osteoporosis and these two results have been associated to indicate that osteoporosis is due to a deficiency of bone protein in the matrix. Thus far, all efforts to maintain patients with osteoporosis on high protein diets and in positive nitrogen balance, when this is possible, have not resulted in a demonstrable increase in density of the bones as measured densimetrically.

I would certainly think we should for the present, until more definite information is forthcoming, assume that osteoporosis involves at least two things, one, a loss in the protein matrix, and two, a loss of mineral salt which impregnates that matrix. Most important of all, we should keep our minds completely free and open as to the real causes of osteoporosis. I believe, myself, that we really know very little about it, and by admitting this freely at least we do not becloud the issue, leaving the way open for further investigation.

Some Metabolic Aspects of Osteoporosis

ANNE C. CARTER AND EPHRAIM SHORR

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Osteoporosis is among the most common metabolic bone diseases. The various etiologies of osteoporosis, the histology and chemical features were briefly discussed. The indices available to evaluate the therapy of osteoporosis are symptomatic improvement, radiologic changes and metabolic balance studies. It has been estimated that between 10 and 30 per cent of the total body calcium is lost before osteoporosis is demonstrable by x-ray. Metabolic studies in subjects with acute anterior poliomyelitis have shown that the earliest x-ray changes,—a patchy demineralization and coarsening of trabecular markings in the lower extremities regional to the joints,—appear with an average loss of 1.9 per cent of the total body calcium.[1] Although total calcium losses during seven months ranged between 4 to 8.5 per cent of the total body calcium, no roentgenologic changes were noted in the spine. Hence, osteoporosis of the spine is not demonstrable roentgenographically unless at least 8 to 10 per cent of the total body calcium is lost.

Metabolic studies in this laboratory during the past twelve years have been concerned with the possible usefulness of strontium as an adjuvant to the remineralization of the skeleton as well as the use of high calcium diets, alterations in the protein content of the diet, and the administration of vitamin D_2, and estrogens alone and in combination with androgens.[2, 3] These studies may be summarized as follows:

1. Strontium is well absorbed and retained without interfering with calcium retention and calcium and strontium retentions are hence additive.

2. Strontium is retained predominantly as the tristrontium phosphate salt.

3. Strontium and calcium retention is favorably influenced by estrogens, androgens and vitamin D_2.

4. Calcium retention is augmented by a high calcium diet.

5. Nitrogen storage is not necessarily the limiting factor to calcium and strontium retention in osteoporosis.

6. Strontium may be a useful tool for the study of the turnover of lime salts in man without the hazards involved in the use of radioactive isotopes.

DISCUSSION

JOHN EVANS: It is a privilege to participate in this program, and I am complimented to have been asked by Dr. Carter and Dr. Shorr to discuss their paper. I hardly feel qualified to discuss the subject of bone metabolism, but Drs. Carter and Shorr have the ability of making the complexities of tissue metabolism understandable even to radiologists. Having apologized for my ignorance of the subject, I can now proceed to discuss it like an expert.

The usual method of appraising bone density from roentgenograms is the subjective impression of the radiologist or research worker. This has the obvious drawbacks of any subjective method of evaluation. In the past, several attempts have been made, notably by Mack,[4] Stein,[5] and Sanders,[6] to develop an objective method of evaluating skeletal mineral content. These involved the use of a stationary beam of light passing through a certain area of bone on an x-ray film into a photronic cell. Because of certain inherent difficulties in the method consistent results were not obtained. Recently, however, Mack, Brown and Trapp[7] of the Ellen H. Richards Institute, School of Chemistry and Physics, The Pennsylvania State College, have developed and tested a microphotometric scanning method for evaluating mineral density of bone. The accuracy of this procedure is based on the validity of two assumptions:

(a) that the photographic density of the image on a roentgenogram is related in a known manner to the density of the mineral of the bone upon which the roentgenogram is based, and (b) that through the use of a step wedge or ladder made of a substance of homogeneous density and generally similar in chemical composition to bone, placed on the film at the time when the exposure is made, corrections can be applied for unavoidable variations in exposure and development technique.

The School of Chemistry and Physics of The Pennsylvania State College has a Bone Density Research and Evaluation Center. This Center provides a service whereby evaluation of bone density from x-ray films can be obtained. The Center has prepared a manual of instructions for Exposing and Developing X-Ray Films for Bone Density Evaluation, a copy of which I have, and which I will be glad to show to anybody who is interested.

The availability of an accurate objective method of evaluating bone density has considerable practical significance in permitting assessment of progress of treatment in such conditions as produce osteoporosis, for example, postmenopausal osteoporosis. It is a well known fact that the conventional roentgenographic method of evaluating remineralization in the treatment of osteoporosis is relatively insensitive in reflecting such changes. This is particularly true of the spine where changes in the magnitude of 60 per cent of the mineral content may occur before any radiographic change becomes apparent.

In the group of patients immobilized by poliomyelitis that Dr. Carter referred to, serial radiographic studies of the skeleton showed minimal evidence of de-ossification at the ends of long bones when the body had lost 2 to 3 per cent of its calcium content. There were, however, no detectable roentgenographic changes in the vertebrae, even when there was marked demineralization of the pelvis and long bones of the lower extremities.

Osteoporosis, when due to a systemic cause, has a predilection for the spine. On occasions one hears the statement that postmenopausal osteoporosis is limited to the spine. This of course is not true. The spine is most commonly and predominantly involved, but the skull and extremities may also be involved. We have known of instances in which the diagnosis of postmenopausal osteoporosis has been rejected because the skull or extremities have been involved. The lamina dura around the teeth is intact, an important point in the differential diagnosis between osteoporosis and osteomalacia. In postmenopausal osteoporosis there can be a good deal of deformity of the spine without symptoms, as Dr. Plimpton has mentioned.

Postmenopausal osteoporosis is the commonest of all forms of osteoporosis. Those cases that have received hormonal treatment because of the severity of their osteoporosis and that have shown improvement in their general clinical well-being have, in our experience, shown no radiographic evidence of increase in bone density, even though total body calcium has been increased 10 per cent or more.

I should like again in closing to draw attention to the manual I mentioned, which I think many radiologists will find very interesting. I think the Bone Density Research and Evaluation Center, Pennsylvania State College, will be extremely helpful in cases that have to be followed over a long period of time as a place where measurements of bone density from submitted radiographs may be obtained.

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NEW YORK PATHOLOGICAL SOCIETY

*Abstracts of Papers and Discussion**

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Studies on Living Human Ova

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Observations have been made by means of phase contrast microscopy in an attempt to gain a more accurate and complete cytologic understanding of living human follicular and tubal ova, before and after their exposure to spermatozoa in vitro.

The follicular ova were aspirated from normal-appearing follicles by means of a syringe and 22 gauge needle. The tubal ova were washed from fallopian tubes immediately upon their removal. The ova were kept at 37° C. either in follicular fluid or in homologous blood serum.

Upon aspiration the follicular eggs were normally surrounded by the corona radiata around which were almost invariably some of the cumulus cells. In almost every case an ovum was obtained from a normal-appearing follicle. The follicular fluid was clear and straw-colored. The largest number of ova obtained from one ovary was sixteen.

Partial dissolution of the corona and cumulus cells occurred after incubation of the ovum in the follicular fluid to which fresh normal semen was added. Complete dissolution of the corona and cumulus cells was obtained after the egg was incubated in the follicular fluid or homologous blood serum to which fresh normal semen and homologous tubal mucosa were added. Experiments with hyaluronidase showed no detectable dissolution of these cells. No dispersion of the cumulus was observed in control ova after twenty-four hours of incubation at 37° C.

The diameter of the largest ovum measured 150 microns to the outer surface of the zona pellucida. Movement of the vitellus within the zona pellucida was often seen in the denuded normal ovum upon slight agitation. The larger ova were eccentric within the zona pellucida, and a definite polarity was demonstrated.

Soon after the semen was added to the follicular fluid, the spermatozoa surrounded the cumulus and corona cells. After denudation, the spermatozoa covered the zona pellucida almost if not completely. In no case was there any evidence of trophic influence of the ovum on the spermatozoa, in that they were observed swimming in the closest proximity to the egg and yet passed right by without any apparent attraction. However, having once accidentally touched the ovum, the vast majority remained in contact with it. The ovum was often moved about within the medium and simultaneously rotated in the clockwise direction by the spermatozoa. The maximum rate of rotation was measured at 360° in fifteen seconds; this continued for over twelve hours. More than one spermatozoon may penetrate the zona pellucida and enter the perivitelline space.

* Manuscripts received July 1954.

The zona pellucida was found invariably to contain interlacing fibrils on which were located dark, fine granules. This fibrillar network adds to the elasticity of the zona pellucida.

The vitelline or cytoplasmic membrane was normally represented by the limiting boundary of the cytoplasm or ooplasm. The cytoplasmic contents were distributed evenly throughout. The completely round germinal vesicle was usually eccentric with a single nucleolus often eccentric within. The nuclear membrane was clearly seen. When dissected free, the nucleolus maintained its intact spherical form.

An entire spermatozoon was photographed within the cytoplasm of an egg containing three polar bodies. Other ova showed one and two polar bodies. An egg dividing into the two-cell stage was observed after thirty hours of exposure to spermatozoa at 37° C., a perfect four-cell stage containing three polar bodies after fifty hours, and an eight-cell stage after sixty hours.

Serous Cystadenocarcinoma of Ovary

CARL T. JAVERT

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A total of 127 cases of serous cystadenocarcinoma of the ovary was reviewed. Of this number, 110, or 87 per cent, of the patients had been followed for five years or longer; sixty-eight, or 62 per cent, had died within five years; eighty-nine had been treated for five years or more; twenty-one, or 24 per cent, lived five years or more. The incidence of serous cancer in the gynecologic cases was about one in 200, while in the obstetrical patients it was one in 27,000 cases.

Thirty-three cases, or 26 per cent, were operable and ninety-four, or 74 per cent, were inoperable, which is the chief cause of a poor prognosis for serous cancer. Distinct factors which govern the prognosis of serous cancer are as follows: (a) operability, (b) stage of the disease, (c) degree of anaplasia and (d) radiation therapy.

Operability was defined as follows:

		Number	*Per-cent*
Operable			
Group A	Complete removal of primary ovarian tumor, unilateral and/or bilateral; no gross metastases	33	25.9
Inoperable			
Group B	Complete removal of primary ovarian tumor with some remaining metastases	77	20.6
Group C	Partial removal of tumor or exploratory laparotomy with or without biopsy; carcinomatosis	17	13.4

Operative mortality was clearly defined and included all deaths occurring from the time of administration of anesthesia, during the operation and postoperatively up to the day of discharge or transfer from the service, without correction for medical or surgical complications. On this basis there were eleven operative deaths, or 8.7 per cent.

The stage of the gross and microscopic extent of the disease can be summarized as follows:

		Number	*Per cent*
Stage 0	Anaplastic changes limited to epithelium	6	4.7
Stage 1	Invasion of capsule	28	22.0
Stage 2	Metastases to pelvic organs only	5	3.9
Stage 3	Metastases to abdominal organs	59	46.5
Stage 4	Carcinomatosis	29	22.8
	Total	127	99.9

Unilateral tumors had a higher incidence of metastases and therefore a poorer prognosis than the bilateral tumors. Therefore, the stage of the disease was not based on unilateral and bilateral involvement, as practiced by other authors. Endosalpingioma, a variety of serous cancer, the "low grade" or "semimalignant" tumor of other authors, was described and discussed. Nineteen cases were so classified, in which eleven of the patients, or 57.9 per cent, lived five years.

The degree of anaplasia was determined according to nuclear size as compared with a formalin-fixed red cell and the total number of cases in each group is as follows:

		Number	*Per cent*
Class 1	Atypical cells about same size as a red cell. The "low grade" or "semimalignant" tumors of other authors, including endosalpingioma	26	20.3
Class 2	Atypical cells twice as large as a red cell	21	16.5
Class 3	Atypical cells three times as large as the red cell	42	33.2
Class 4	Atypical cells four times as large as the red cell and also pleomorphism. The "sero-anaplastic" or embryonal carcinoma of other authors	38	29.9
	Total	127	99.9

In general the anaplastic, class 4 cancers occurred in the older women, whereas class 1 tumors, or "endosalpingiomas", were found in the younger patients. Patients with anaplastic, class 4 tumors also had more widespread metastases and obviously a poorer prognosis.

The five year survival rates, according to operability, were as follows:

Operable	
Group A	64 per cent
Inoperable	
Group B	32 per cent
Group C	0 per cent

The five year survival rates, according to stage, were as follows:

Stage 0	100 per cent
Stage 1	45 per cent
Stage 2	33 per cent
Stage 3	15 per cent
Stage 4	0 per cent

The five year survival rates, according to anaplasia, were as follows:

Class 1	73 per cent
Class 2	25 per cent
Class 3	11 per cent
Class 4	3 per cent

The effects of radiation therapy were discussed. The best results were obtained in the operable group of thirty-three patients, with a gross survival rate of 78.5 per cent, versus only 44.4 per cent in patients not irradiated. Radiation therapy appeared to prolong life for a short time in the advanced cases, but it did not alter the course of the patients regarded as hopeless.

Only four asymptomatic cases were discovered on routine pelvic examination. It was estimated that approximately 10,000 women must be examined routinely to diagnose one case of serous cancer. Therefore early diagnosis is impractical, with our present methods.

Exploratory laparotomy through a low midline incision, with a total hysterectomy, bilateral salpingo-oophorectomy whenever feasible, together with resection of the omentum and selective removal of pelvic lymph nodes as indicated, is the operation of choice for serous cancer. Of six patients subjected to partial lymphadenectomy, two, or 33 per cent, had nodes that contained metastases. This aspect of the problem obviously needs further investigation and undoubtedly influences the prognosis.

DISCUSSION

HARRY W. BURNETT: From the standpoint of the radiologist, we are much concerned with prognosis, and we are constantly confronted with the question of the advisability of treating a given patient. As Dr. Javert mentioned, we have to have definite criteria upon which to base a decision. In going over the articles written, it is evident

that many of them include all types of ovarian carcinoma in reporting five year survival figures. In the early portion of an article there is usually a breakdown of the cases into different categories, and then the results appear rather limited when all cases are evaluated together. I think Dr. Javert is to be commended for having selected an outstandingly important lesion of the ovary and discussed that one entity. He has discussed various factors that have been demonstrated to influence prognosis. He has also shown the unreliability of certain factors such as unilateral versus bilateral involvement. I think also it is very important that he discussed the entity of endosalpingioma. Although he mentioned that a number of patients lived from fifteen to thirty years after diagnosis, a good many of them died within five years, so apparently the endosalpingioma has to be included among the malignant lesions. Although the outlook in carcinoma of the ovary, particularly this type of cystic carcinoma, is not very hopeful, when various categories are established, as Dr. Javert has done, it is possible to give a more encouraging prognosis for certain of the groups of cases. Frequently it is stated that radiation is only palliative, and in many cases it is given as a last resort. This is true in regard to the highly anaplastic, widely disseminated inoperable tumor, but the picture is actually encouraging in regard to the cases in Dr. Javert's operable group A. The five year survival is 64 per cent for the entire group, and out of that group, in those who were treated by surgery alone, the survival rate was 42 per cent. This group had surgery alone and no radiation because it was thought that sufficient treatment had been given, so radiation was not employed. Dr. Javert showed a survival rate of 78 per cent in the operable group, in whom it was thought there was likelihood of residual cancer, and who therefore were referred for radiation. In this group the survival rate rose to 78 per cent, almost doubling the survival rate of the non-irradiated group. I think in the future it would be worth while to radiate more of the patients in the operable group.

In regard to the treatment of patients with more advanced lesions, many of them do live for from one to three years, and in that period of time they can experience considerable comfort if radiation is employed to postpone the appearance of ascites, or reduce its amount. Further work is being done on these patients, not only with external roentgen radiation, but also with radioactive gold.

It is interesting that in Dr. Javert's 127 cases, nineteen were classified as endosalpingioma, an incidence of 15 per cent. Out of eighty-nine cases which it was possible to follow for five years, twenty-one patients survived. Of those twenty-one, eleven were cases of endosalpingioma. This represents 52 per cent of the survivors of the entire series, which stresses the value of accurate diagnosis.

CHARLES T. OLCOTT: I can only accept Dr. Javert's statement that he is not a pathologist in the sense that his activities are not limited to pathology. He is considered an excellent pathologist by those of us who work with him at the New York Hospital-Cornell University Medical Center. I am very much interested in his correlation of the clinical and pathologic material in these cases.

PAUL KLEMPERER: I would like to ask a practical question for guidance. I believe, Dr. Javert, that there are in your material some cases which in former years we would have called cystoma with the question whether it is already a definite papillary cystadenoma, which can be decided by histologic examination only. How do you handle these cases? Do you believe that they belong to the group of ovarian malignancy if they show one or two small areas in which there is evidently more striking cell proliferation than in the other parts? Are these already tumors in which you advocate bilateral oophorectomy and hysterectomy, and if so, when and how do you make the diagnosis? Do you require frozen section for decision, or do you make the decision on your own gross examination? I think that is a practical question; we are called so frequently to the operating room to make the decision whether the surgeon should do a radical operation in the case of a young woman. I want to be assured that these tumors are only semimalignant. The malignancies are quite evi-

dent; it is the borderline group about which I should be grateful for information.

CARL T. JAVERT: I am grateful to you, Dr. Klemperer, for your discussion, because you have had a much greater experience than I have. Frequently I am called to the operating room when a surgeon has this problem. If the patient is a very young girl, rather than prepare a thick frozen section in the operating room I prefer to examine the ovary, express an opinion as to its being benign or malignant, and the operator proceeds accordingly. Meanwhile, the specimen is fixed promptly, and put into the autotechnicon. The next day we have paraffin sections. I despise frozen sections. Maybe I am in good company. I think frozen sections should be outlawed, because they are often too thick. The patient's future should not hang on a quick diagnosis of cancer by frozen section, for sometimes the better paraffin section may reveal a benign lesion. This happens in all good hospitals and makes me inclined to wait in the case of a young girl, who is perhaps unmarried and has hopes of having children. These and other intangibles which go into the clinical management of a case should be considered, and priority should not be given to frozen sections. I think we would agree with you on that, Dr. Klemperer. After we have microscopic proof of cancer we can always reoperate. We have re-operated in only a few of these cases. Many of the so-called benign endosalpingiomas are in this category.

ALFRED ANGRIST: I would like to pursue the practical aspects of this problem by asking Dr. Javert whether he can give us the prediction by the normogram of external implants, particularly for the more benign tumors, endosalpingiomas, and whether he has had the experience of seeing widespread tumors regress, as the older literature stresses.

CARL T. JAVERT: Marchetti[1] reported on this in 1941; he had a number of cases, and we have added little to his initial study. You may recall the article. Up to that time the endosalpingiomas had been considered benign. Marchetti had no reason to think otherwise, and he excluded them from his study. I think he had nine cases, and subsequent experience has led us to bring the sum up to nineteen, and those patients have had widespread metastases. From the standpoint of this facetious normogram they would probably be placed in neoplasia class 1, although from the standpoint of widespread metastases we would also have to put them in stages 3 to 4. Even so, the line crosses at 50 per cent, which is just about what we are getting in our five year survivals. A good many are dead in five years, and yet we have had eleven of nineteen who lived five years or more. Some of the patients die after ten years, and Dr. Olcott autopsied one who died after thirty-four years. You can exclude the endosalpingiomas if you wish and say they are not cancer. This would make our five year survival figure even worse, something like 11 per cent. It is not good at all: clinically no one is seeing the patients early enough. I talked on this subject last month in Florida and no one offered any suggestions for early diagnosis, either by cytologic smear or blood serum analysis. I suggested that we teach husbands to do pelvic examinations twice a year; perhaps that would help. They have become quite learned from their natural childbirth courses! Why not go a step further?

J. M. RAVID: In discussing the serous papillary cystic tumors of the ovary, it seems to me that we ought to mention also the pseudomucinous variety. For the sake of expediency, I presume, Dr. Javert could not discuss them this evening. I should like, therefore, to ask Dr. Javert whether in his experience there is any difference between these two varieties of ovarian tumors as far as the prognosis is concerned. It is my impression that although histologically there is a great difference between the two, from the point of view of their behavior or prognosis they differ very little. Not infrequently the pseudomucinous tumors may appear histologically quite innocent, or of low-grade malignancy, and actually they behave in a most malignant fashion.

I should also like to ask Dr. Javert about the classification of his series of cases. I wonder whether his new grading method, in

which he uses the size of the nucleus as the chief criterion is helpful in other tumors as well. It seems to me that the other histologic criteria, such as the number and degree of differentiation of the epithelial layers, pleomorphism of the cells and nuclei, and other features may be of greater help in judging the degree of malignancy of the ovarian tumors. On the other hand, judging from the vagaries and inconsistencies in the behavior of ovarian tumors in general, perhaps it may even be wiser to abandon their histologic grading altogether.

CARL T. JAVERT: To answer the last question first, I despise grading of tumors; maybe you do, I hope you do. We have found no correlation in grading cancer of the cervix or of the endometrium. We do not do it any more, and yet somewhat paradoxically we do grade these ovarian tumors. We have had some experience in realizing that it is not as good a yardstick as it may have appeared on the screen. I am not advocating it at all, but I was interested in the fact that Broders has not written on the grading of these tumors. The criteria you mentioned we also use. We are in the process now of analyzing the pseudomucinous cystic tumors, benign and malignant, and have not arrived at any opinion yet. In *Cancer* there is a recent article from the Mayo Clinic concerning some 500 patients whom they studied.[3] In our Department the serous cystadenocarcinoma accounts for about 75 per cent of our ovarian carcinomas, so we thought it important to study this histologic type first, and not confuse the picture with granulosa cell tumors, malignant dermoids, and other cancers of the ovary. The problem is similar to Taussig's famous study of carcinoma of the vulva.[2] He included cancer of Bartholin's gland with those of the urethra and epitheliomas of the vulva. This is not the way to do it, as clinicians see it. The same tendency to lump cancers exists in studying those of the breast; all cancers of the breast are thrown into one category clinically. We expect different histologic cancers to behave differently biologically. They may have different radiation responses. We should begin by thinking of explicit diagnosis, and that is why we thought of selecting this specific group—serous carcinoma of the ovary—for presentation this evening. A more complete discussion with illustrations has been published elsewhere.[4]

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Pathologic Observations on Atelectasis with Hyaline-Like Membranes

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The development of a special field of pathology is often necessary when new clinical problems arise. Human reproductive pathology is one of the branches of pathology which now needs improvement and advancement. Perhaps in no field is there as much demand for integrated basic science as in the study of the adaptation of the fetus to its environment. Knowledge of fundamentals such as metabolism, fluid and electrolyte balance, regulation of temperature, antigen-antibody reactions, and biologic variations of cells reaches its zenith in human reproductive pathology.

One of the pertinent problems at the moment regarding death of the liveborn infant is atelectasis associated with hyaline or hyaline-like membranes. In the United States approximately three to eight infants per 1000 live births die of this condition. In order to dispel the idea that pulmonary hyaline membranes are limited to the newborn, a review of twenty-one diseases of adults and older children in which the condition has also been reported is included. The best known of the group are influenza, war gas poisoning and rheumatic disease. The suggested etiology in practically all of the adult diseases, in contrast to the newborn, was vascular injury, particularly of the alveolar capillaries. In the neonate numerous causes have been advanced, including the aspiration and dispersion of amniotic fluid protein, infection, desquamation, congenital malformation of the lung, intrauterine anoxia, aspiration of vernix, and more recently, oxygen poisoning. In general two basic concepts have been developed for the origin of pulmonary hyaline-like membranes. First, the inhalation of amniotic fluid with continuous concentration of protein about the respiratory bronchioles, alveolar ducts and alveoli; this protein, after the infant is born and has breathed, produces obstruction and leads to atelectasis. The second concept hinges on the derivation of the protein material from the blood rather than the amniotic fluid. This concept would be supported by the occurrence of numerous diseases in older children and adults, including oxygen poisoning in which vascular damage, particularly of capillaries, is believed responsible for the accumulation of protein.

The clinical picture of this condition is well known. An infant, usually with spontaneous respiration at birth, breathes normally for one or two hours. After this the respirations become difficult with increasing dyspnea and cyanosis. Marked retraction of the ribs and sternum occurs, but there is some difference of opinion as to whether the infant is having a protracted inspiratory effort or a difficult expiratory phase of respiration. Death takes place in a few hours or two or three days. The maternal and fetal complications which have been associated in higher frequency with this disease are 1) maternal diabetes, 2) cesarean section, 3) prematurity, 4) breech delivery, 5) multiple pregnancy, 6) toxemia.

It is important for the pathologist to differentiate the degrees of atelectasis in the newborn lung. In the past the following methods have been used:

1. Measurement of the thickness of the alveolar walls.

2. Counting the number of alveoli in one square millimeter of the lung. Usually five different millimeter areas are averaged.

3. Counting the number of epithelial-lined bronchioles per low power field of the microscope.

4. Comparing the areas of lung tissue to the areas of the alveolar spaces expressed as a percentage.

The fourth method has been used in the

Obstetrical Pathology Laboratories of the Johns Hopkins Hospital with some degree of success. At least 40 to 50 per cent of the lung sections should be lung tissue as compared to the alveolar spaces, before the primary cause of death would be classified as atelectasis. Similarly, some basis for grading or comparing the degree of pulmonary hyaline or hyaline-like membranes in the newborn lung was necessary. The following arbitrary grading system was devised:

Grade I: Scattered, irregular, thin membranes in a few alveolar ducts and alveoli.

Grade II: Thin membranes with wide distribution in alveolar ducts and alveoli.

Grade III: Thicker membranes, well distributed in at least 75 per cent of the expanded alveolar ducts and alveoli.

Grade IV: Very thick membranes in all expanded alveolar ducts and alveoli.

Numerous examples of the degree of atelectasis and grading of the hyaline membranes were illustrated with photomicrographs. One of the major problems associated with atelectasis and hyaline membranes is the proper use of terminology in classification. At the present time the following nine terms are used to classify perinatal deaths:

I. Anoxia
   - Placenta
   - Cord
   - Maternal complications
   - Complications of labor

II. No abnormal state
   - Without maternal disease
   - With toxemia
   - Other acute and chronic disease
   - Diabetes

III. Birth injury

IV. Malformation

V. Abnormal pulmonary ventilation

VI. Infection
   - Syphilis
   - Other infection

VII. Erythroblastosis

VIII. Therapeutic interference

IX. Other conditions or causes

Ordinarily atelectasis associated with hyaline-like membranes is classified under "Abnormal Pulmonary Ventilation." However, it was pointed out by numerous case illustrations that it is very difficult to classify some infant deaths properly in cases of severe maternal anoxia, malformation or intrauterine infection in which the lungs may exhibit histologic details similar to the findings with atelectasis and hyaline-like membranes. Among 137 autopsies in which there were hyaline membranes, in only seventy-four were there sufficient atelectasis and hyaline-like membrane to consider the pulmonary findings as the primary cause of death.

Up to the present time approximately five basic methods have been used to produce pulmonary hyaline-like membranes in experimental animals. They are 1) intratracheal injection of amniotic fluid and foreign substances; 2) bilateral vagotomy; 3) oxygen poisoning; 4) carbon dioxide poisoning; 5) x-ray irradiation. Although numerous investigators have been able to produce pulmonary hyaline membranes, they have rarely succeeded, as far as we can ascertain, in the production of any appreciable degree of associated atelectasis. As previously emphasized, since the latter condition is part and parcel of the pathologic condition as seen in the human, there would seem to be room for questioning whether the membrane thus far produced in laboratory animals bears any relationship whatever to the pathologic picture met at autopsy in cases of neonatal death.

In an effort to add information relative to this difficult problem two species of animals, hooded rats and guinea pigs, were submitted to the following procedures:

1. Varying concentrations of oxygen (85 to 95 per cent) under normal atmospheric pressures.

2. Varying oxygen concentrations with pressures simulating the Bloxsom infant air lock cyclic pressure (one to three pounds per square foot).

3. Bilaterial cervical vagotomy associated with and without superimposed oxygen poisoning.

4. Carbon dioxide poisoning.

5. Oxygen poisoning with superimposed tracheal and bronchial obstruction.

All five of the methods used were successful in the production of pulmonary hyaline-like membranes. The guinea pigs developed pulmonary hyaline-like membranes with greater ease than the rats. In thirty-eight

adult rats nineteen, or 50 per cent, developed pulmonary hyaline-like membranes as compared to forty-five adult guinea pigs in which forty-three, or 95.7 per cent, developed pulmonary hyaline-like membranes. Although some degree of patchy atelectasis occurred in many of the animals, the picture analogous to that of the human newborn with atelectasis was not attained unless partial or complete tracheal obstruction or artificial pneumothorax was performed.

Eleven stillbirths and nineteen neonatal deaths were studied. Of the eleven stillbirths, four occurred when the mother had been in oxygen (90 to 95 per cent) and normal pressure conditions; two died in oxygen-poisoned mothers in the Bloxsom apparatus with one to three pounds cyclic pressure. Three additional stillbirths occurred in mother guinea pigs in which bilateral cervical vagotomy had been performed, and in two other fetuses of a mother who died with carbon dioxide poisoning. Although the mothers of the eleven stillborn fetuses demonstrated excellent pulmonary hyaline-like membranes, not one of the fetal lungs had a membrane.

Among nineteen guinea pigs who died in the neonatal period the results were quite different. Some degree of atelectasis associated with hyaline-like membrane formation was produced in eleven (57.9 per cent) of the nineteen guinea pigs. In thirteen full term guinea pigs membranes were formed in nine (69.2 per cent). Although oxygen poisoning will produce hyaline membranes in adult guinea pigs and rats there is rarely any associated atelectasis. Newborn guinea pigs and rats, however, react to oxygen poisoning with development of the full picture, of hyaline membrane plus atelectasis, in the majority of cases. This suggests some special predisposition on the part of the newborn lung to this entity. The use of experimental oxygen poisoning is an experimental device which turns the direction of research to more integration of the etiologic factors in the development of atelectasis with hyaline-like membranes. It is possible that disorders of circulation, capillary damage, or even antigens antibody reactions may exist and therefore intensive studies on lung capillaries and capillary permeability are needed.

Histochemistry has been employed by the author and his associates. The membranes in newborn lung are usually fat-positive, negative for iron, collagen, amyloid, serum protein, red blood cells and mucus; positive for polysaccharide aldehyde. Approximately thirty different histochemical procedures have been used but the exact chemical structure of the membranes has not been elicited. This problem is analogous to the one that prompted Klemperer's long investigation of the histochemistry of hyaline thrombi in the glomerular capillary lumina in systemic lupus erythematosus.

The problem of atelectasis with hyaline-like membranes has reached that stage in human knowledge beyond the simple descriptions of structures visible under the light microscope. Like so many problems it has transcended the stage of purely descriptive pathology and its solution may have to be aided by the study of intimate physical, chemical, and metabolic processes. In recent years new medical advances have occurred so rapidly that it is almost impossible for any one person to relate the findings in one field to another with equal rapidity. The solution of the problem of atelectasis with hyaline-like membranes is just one of the unsolved problems in the pathology of human reproduction.

DISCUSSION

ANDREA SACCONE: I had occasion in the last month to perform autopsies on several newborn babies who died a few hours after delivery by cesarean section. In all the cases I found edema of the meninges, in some cases with little edema of the body and some pathologic conditions in the lungs, similar to those described by Dr. Potter in her book "Pathology of the Fetus and the Newborn."[1] I would like to report the case of a patient thirty-two years old with three previous pregnancies. She had one abortion at three months gestation and one baby was delivered by cesarean section three and a half years ago because of a contracted pelvis. In this patient a low cesarean section was performed on the fourth of March and a male child was delivered, apparently normal, weighing approximately 7 kilograms. The baby was born at 11:10 A.M.; at 12:20 P.M.

he became cyanotic and the respiration became labored. Aspiration was used repeatedly and the baby was placed in oxygen. He expired at 10 P.M. the day of birth.

At autopsy there was an increase of intracranial fluid; more than 50 cc. of cerebrospinal fluid was obtained from the head. The lungs had a peculiar appearance. They were very well expanded, but had a hepatized appearance and were of a uniform dark reddish purple color, like that described by Dr. Potter. The histologic examination revealed a hyaline-like membrane and resorption atelectasis, as presented in the slide shown. The air spaces were almost lined by an irregular layer of homogenous eosinophilic material. Many distal alveoli were collapsed, in spite of attempted insufflation of air. This picture corresponded completely to the description by Dr. Potter. The lungs were put in water and sank, in spite of the fact that the baby had lived a few hours. This hyaline membrane after cesarean section is always associated with anoxia. I believe that the hyaline membrane must be a consequence of anoxia. I would like Dr. Anderson to tell us something about that.

GEORGE ANDERSON: I can only agree with Dr. Saccone. I wish I could say something positive about that. We are systematically submitting the brains of all our newborn infants to complete serial sectioning, about 1600 sections in a brain, and hope some day that we will be able to say whether or not the phenomenon described by Potter can be verified. The cesarean section baby, even were it to die of other causes, has more cerebrospinal fluid over the surface of its brain than the baby delivered by vagina. This finding has been linked to the simple fact that the pressure of the birth canal tends to eliminate the cerebrospinal fluid, but whether that explanation is too simple I think is an unsolved problem. We must also keep in mind the higher centers of control of the respiratory apparatus. I have seen this association, but the only way today of checking on anoxia would be to have blood oxygen determinations at the moment of birth. We know the presence or absence of cyanosis is not the most final proof for saying a baby has or has not hypoxia, and if we had observations that could be proved they might be a clue to the problem. I do not believe I am in a position to deny or support this premise at this point of our knowledge.

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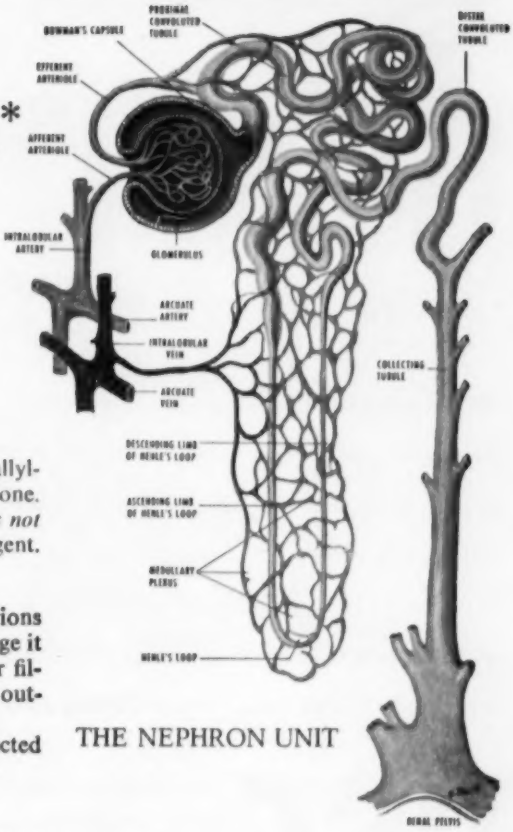

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HERBERT C. MAIER — *Assistant Clinical Professor of Surgery, College of Physicians and Surgeons, Columbia University; Director of Surgery, Lenox Hill Hospital*

HAROLD E. B. PARDEE — *Assistant Professor of Clinical Medicine, Cornell University Medical College; Attending Physician, Cardiology, Polyclinic Hospital*

ERNEST L. WYNDER — *Assistant Professor of Preventive Medicine, Sloan-Kettering Division, Cornell University Medical College; Head, Section of Epidemiology, Sloan-Kettering Institute*

Fifth Meeting — Third Series

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Subject: **PARKINSON'S DISEASE: MEDICAL AND SURGICAL MANAGEMENT**

Moderator:

SAMUEL BROCK — *Professor of Neuropsychiatry, New York University Post-Graduate Medical School; Director of Neuropsychiatry, Beth Israel Hospital*

Panel Members:

KATE CONSTABLE — *Assistant Attending Neurologist, The Presbyterian Hospital; Neuropsychiatrist, The New York Infirmary*

IRVING S. COOPER — *Assistant Professor of Neurosurgery, Department of Neurosurgery, New York University Post-Graduate Medical School*

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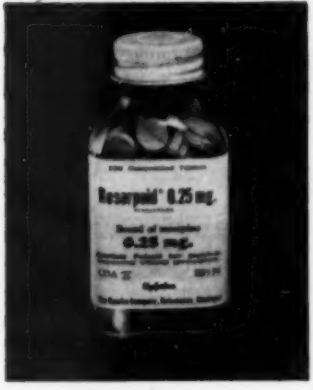

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1. McHardy and Browne: Sou. Med. J. 45:1139, 1952. 2. Lorber and Shay: Fed. Proc. 12:90, 1952.

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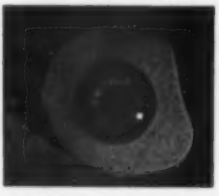

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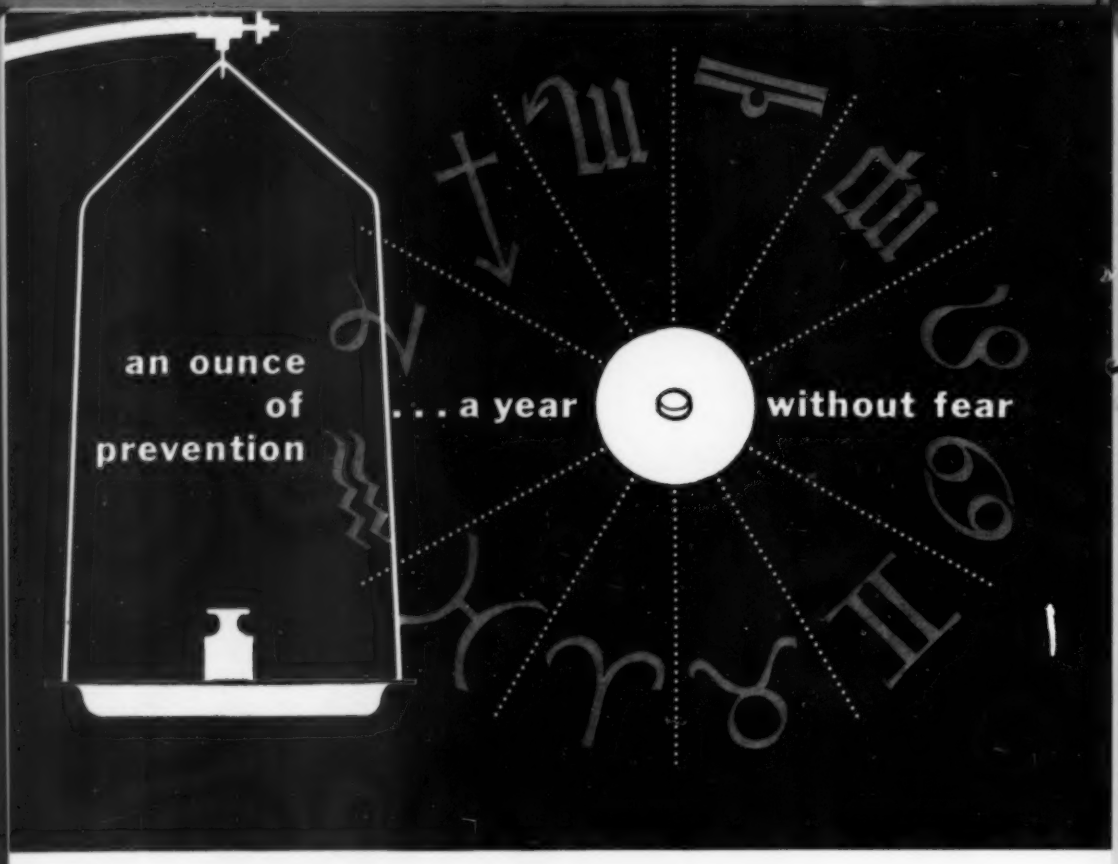

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1. Russek, H. I.; Urbach, K. F.; Doerner, A. A., and Zohman, B. L.: J.A.M.A. *153*:207 (Sept. 19) 1953. 2. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 3. Plotz, M.: New York State J. Med. *52*:2012 (Aug. 15) 1952.

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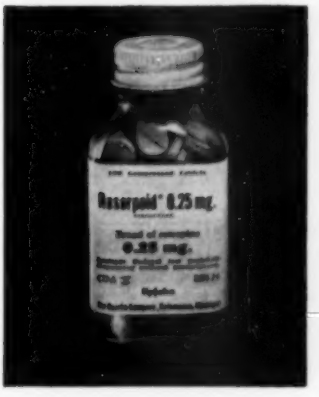

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